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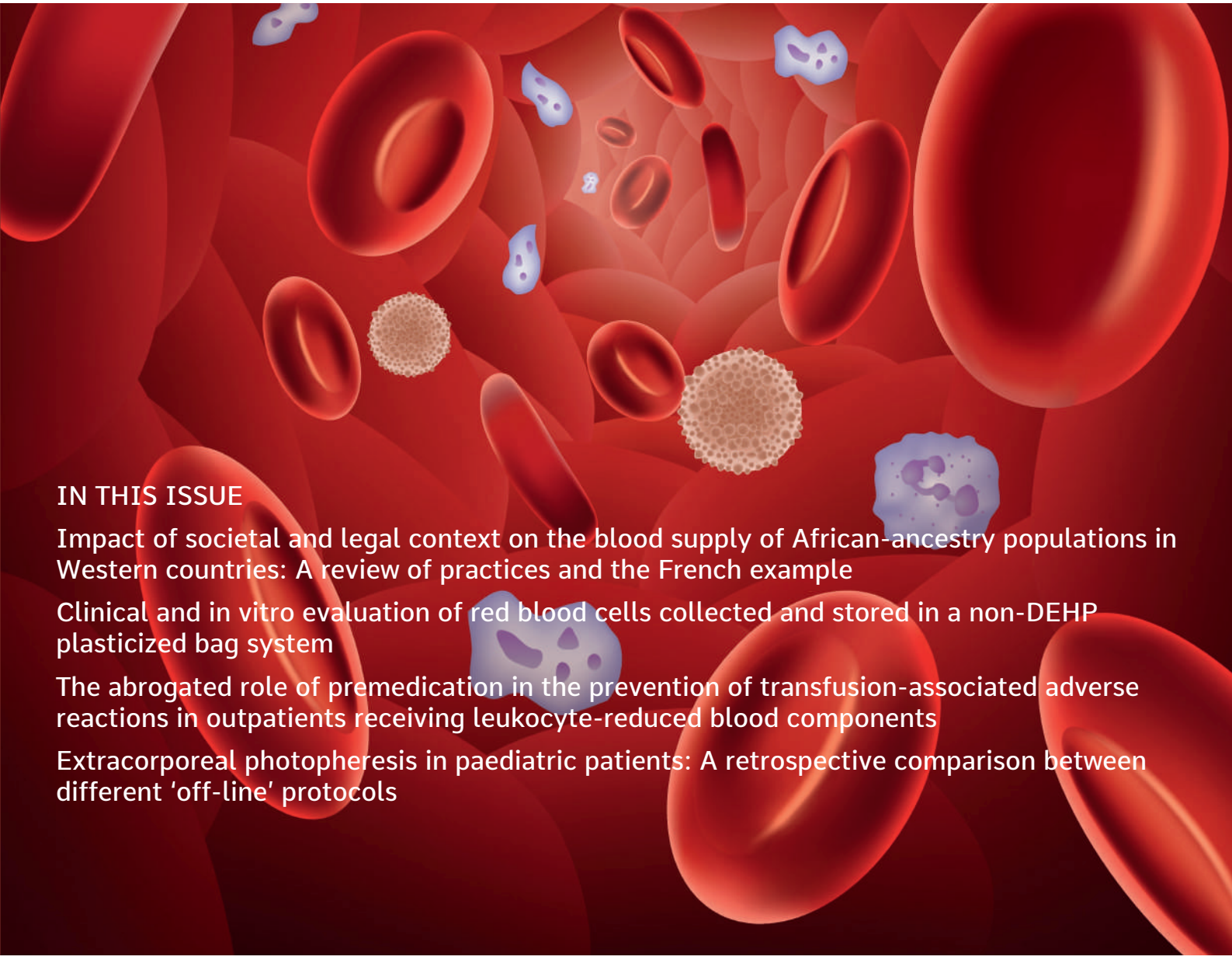

IN THIS ISSUE

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ISBT International Society of Blood Transfusion

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International Journal of Blood Transfusion

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Vox Sanguinis

International Journal of Blood Transfusion

Aims and Scope

Vox Sanguinis reports on all issues related to transfusion medicine, from donor vein to recipient vein, including cellular therapies. Comments, reviews, original articles, short reports and international fora are published, grouped into 10 main sections:

1. Blood Component Collection and Production: Blood collection methods and devices (including apheresis); blood component preparation; inventory management; collection and storage of tissues; quality management and good manufacturing practice; automation and information technology; plasma fractionation techniques and plasma derivatives;
2. Cellular Therapy: Cell-based therapies; CAR T-cell therapies; genetically modified cell therapies; cellular therapy (sources; products; processing and storage); stem cells; cell-based regenerative medicine; cellular immunotherapy; molecular therapy;
3. Donors and Donations: Donor recruitment and retention; donor selection; donor health
4. Haemovigliance: Adverse events in blood and blood component donors and transfusion recipients; corrective and preventive measures of complications; near-misses and errors in the transfusion chain; evaluation and outcomes of adverse events
5. Immunohaematology and Immunogenetics: autoimmunity in haematology; alloimmunity of blood; pre-transfusion testing; complement in immunohaematology; blood phenotyping and genotyping; genetic markers of blood cells and serum proteins: polymorphisms and function; parentage testing and forensic immunohaematology;
6. International Forum: Section in which topics related to any aspects of the transfusion chain (from technical to scientific, including socioeconomic and ethical facets) are discussed by invited participants and summarized by guest editors
7. Patient Blood Management: Bloodless surgery; preoperative anaemia; minimizing blood loss during surgery; alternatives to blood transfusion;
8. Review: Comprehensive reviews or short comments of any aspect related to transfusion medicine;
9. Transfusion Medicine: Transfusion indication, transfusion practice, thresholds and audits; transfusion efficacy assessment, clinical trials; therapeutic apheresis;
10. Transfusion-transmitted Disease and its Prevention: Identification and epidemiology of infectious pathogens transmissible by blood; donor testing for transfusion-transmissible infectious pathogens; bacterial contamination of blood components; pathogen inactivation;

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Contents

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Letter to the Editor

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REVIEW

Vox Sanguinis ISBT International Society of Blood Transfusion

Impact of societal and legal context on the blood supply of African-ancestry populations in Western countries: A review of practices and the French example

Pauline Oviedo[1,2] | Yannick Jaffré[3] | Bruno Danic[4,5] | Stéphane Mazières[1] | Jacques Chiaroni[1,2,5]

[1]Aix Marseille Univ, CNRS, EFS, ADES, UMR 7268, Marseille, France

[2]Etablissement Français du Sang PACA Corse, "Biologie des groupes sanguins", Marseille, France

[3]Aix Marseille Univ, CNRS, UMI3189, Marseille, France

[4]Etablissement Français du Sang Bretagne, Rennes, France

[5]Etablissement Français du Sang Socialab, Saint-Denis, France

Correspondence
Jacques Chiaroni, Etablissement Français du Sang PACA Corse, 149 Boulevard Baille, 13005 Marseille, France.
Email: jacques.chiaroni@efs.sante.fr

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Abstract

In Western countries, blood supply agencies encounter impediments in providing blood groups defined as rare or of interest, notably for sub-Saharan African ancestry (SSAA) recipients. To establish warning levels and anticipate future blood needs, an estimate of the current carriers of rare blood groups, both potential patients or donors, is crucial but complex. Indeed, if the strict needs can be estimated in medical terms, the modalities of blood product collection must be considered from an interdisciplinary perspective, at the interface of biological data and social norms. Here, we aim to understand how legal choices and a set of representations of otherness may influence the supply of rare blood for SSAA populations. After examining these issues, considering different norms and limits that govern French society, we compare this data with those of four Western countries facing the same difficulties (United States, United Kingdom, Italy and the Netherlands). This work began as part as the reflections of Social Lab, an institutional programme created by the French Blood Establishment (EFS). How can we effectively improve the qualitative blood coverage for SSAA populations? There is no unique solution, but there are many more or less effective answers. Comparison across countries reveals a strong influence of the socio-political histories and ethical choices before technical and medical considerations. We consider that an institutional policy is required to resolve recruitment issues of SSAA donors sustainably. Lastly, we introduce a working group called the EFS Social Lab, which aims to set up a monitoring mechanism for donors and societal trends to make blood donation effective.

Keywords

anthropology, donor motivation, donor recruitment, donors, ethics, social norms

Highlights

- Specific societal contexts of each countries affect differently blood donation, particularly in terms of the ethical and legal representation of 'otherness'.

- Rather than subsuming populations with African ancestry into a single ethnic group, an in-depth knowledge of those populations involved is required to improve blood donation.
- The creation of Social Lab, a French institutional initiative to use medical humanities sciences in the monitoring of donors and social trends, will help in this endeavour.

WHY A CLOSE ATTENTION TO SUB-SAHARAN AFRICAN ANCESTRY POPULATION?

Globalization contributes to the deterritorialization of populations, both as cause and effect. Today, about 3.4% of the world population, totalling 258 million international migrants, do not live in their places of birth [1]. Migration routes follow the former colonial political areas and present linguistic communities and idealize the Western countries [2–4]. In France, migrations originate mainly from Africa (47.5% of immigrants), of which 18.3% are from sub-Saharan Africa [5]. Here we refer to the French sub-Saharan African ancestry (SSAA) population, the diversified immigrants and descendants of sub-Saharan origin who live in metropolitan and overseas France. This population was and is motivated to migrate by a multitude of motives, and they have different administrative statuses (i.e., recent or long-term migration, permanent or temporary arrivals), nationalities and the number of generations since arrival [6, 7]. Socially, the entanglement between the country of origin, ages, administrative status and access to citizenship builds an extremely complex patchwork of infinite cultural and political variations [8]. However, though diverse in their identities and backgrounds, the French SSAA population shares biological links with the sub-Saharan African subcontinent. The hiatus between the almost immobile time of genetic transmission and the extreme variability of social situations is not without consequences for blood transfusion. It generates haematological management problems related to migration, explicitly concerning rare blood groups (RBGs).

In France, RBGs have a frequency of less than 1/250 in the general population and no alternative for transfusion compatibility by another blood group. RBGs refer to the following situations: (1) rare blood phenotypes per se, defined by a private, low-frequency or absence of a public antigen (e.g., the Dantu MNS25 antigen, the 700 series or the lack of RH:18 and 19) and (2) relative rarity, related to the uneven geographical repartition of phenotypes [9]. If all human populations are considered, SSAA populations are more exposed to rarity consequences after migration to Western countries. The genetic diversity of African populations is the highest of any population in the world, mainly caused by a longer pre-historic incubation followed by drip out-of-Africa expansion. Moreover, SSAA populations are largely carriers of red cell abnormalities in response to selective pressures of malaria, such as membrane protein polymorphisms, enzymatic disorders and haemoglobin variants [10]. Notably, one of the latter is responsible for sickle cell disease requiring sustained and complex transfusion therapy [11, 12]. The healthcare challenge results from this tension between necessity and scarcity, between, on one hand, a demographic increase of SSAA populations in Western countries with specific haematological characteristics, and, on the other hand, blood product supplies under pressure and sometimes insufficient to handle some distinctive pathologies and the daily health events (childbirth, accidents and surgical procedures).

To ensure self-sufficiency in rare blood products in response to growing demand, it is crucial to have adequate stocks of the targeted blood and, therefore, upstream recruitment of SSAA donors. Effective recruitment intricately involves medical and social dimensions. Here we want to focus on the social aspect, which influences both supply and demand of blood products. Availability of rare blood products requires anticipation and requisite expertise to assess future needs from quantitative and qualitative perspectives. We seek to understand how legal choices and representations of otherness may influence the supply efficiency of rare blood for the Afro-descendant population and what resources organizations have to deal with these availability issues. Finally, we present the strategy adopted by the French Blood Establishment (EFS) to improve availability based on social trends.

THE DIFFICULTIES OF AN ETHNIC CENSUS AND COMMUNITY DONOR RECRUITMENT

Foremost, to correctly assess the level of the stocks of RBG concentrates required, we must evaluate the needs and human resources present in France and thus have demographic data tagging 'African ancestry'. While it is neutral and easy to define biologically, it is more complex to handle sociologically and legally. In France, the legislation stipulates that 'it is forbidden to process personal data revealing the alleged racial or ethnic origin [...]' [13]. Meanwhile, by decision no. 2007-557 DC of 15 November 2007 (act relating to the control of immigration, integration and asylum), the French Constitution Council prohibits 'the processing of personal data that directly or indirectly reveals the racial or ethnic origins of individuals and the introduction of variables of race or religion into administrative files. This applies to the identification directory of natural persons'. Only studies on the measurement of the diversity of origins, discrimination and integration based on objective data such as geographical origin or nationality before French nationality, or subjective data, such as the 'feeling of belonging', are authorized. While these legal and ethical precautions help in avoiding various forms of discrimination, they complicate the assessment of the size of populations with RBG. If a character-based census of individuals is per se possible, it would indirectly reveal the

ethnic origin, which is illegal as stipulated before. Moreover, it would not distinguish the double descendants of African immigrants—homozygous Africans—from those with an African surname but from admixed 'domino couples' who are genetically heterozygous and so are unlikely to carry an RBG. In practice, there are indirect ways to obtain an estimation. EFS is allowed to register the birthplace of the donors and point out the geographical origin through a computer flag. This makes it possible to implement additional biological screening to search for rare phenotypes and genotypes.

Therefore, RBG needs estimation relies on the 'rare blood network', a dedicated process that monitors data related to the delivery of phenotypes considered to be of interest, the number of sickle cell patients (10,000 currently with 400 births per year), the number of active blood donors with phenotypes of interest and the stocks of frozen red blood cells. However, this piecemeal research does not allow for a precise estimate of current and future needs. It is possible to operate legally, but on the margins and by benevolent tracking of donors. This discordance between ethical precautions and the lack of biological precision to identify low-frequency blood phenotypes restrains proactive policies for RBG needs.

The other main limitation of blood product availability is blood collection and, hence, the modalities of donation. In Marseille, where we operate [14–16], in France [17], but also in Europe [18, 19] and in other Western countries [20–27], studies have documented the blood donation determinants of various SSAA populations and highlighted low participation of both occasional neo-donors and recurrent blood donors. Furthermore, the representation of the body and its tissues (blood and organs), as well as the normative systems (e.g., misplaced belief that religions discourage blood or organs donation) are essential but in no way subsume all the factors determining the behaviour of donors.

Indeed, donor behaviour includes socio-political dimensions linked to migration, such as cognitive and practical difficulties to give blood in case of linguistic precariousness and administrative irregularity. The positive correlation between blood donation, social inclusion and even the acquisition of citizenship has previously been shown [15, 26, 28, 29]. If the act of giving inscribes the person in a relationship that includes a counter-gift in return, or at least a recognition of the act [30], what reciprocity or recognition a person might expect when he(she) is precisely not admitted to reside and live in the political space where he(she) stays? A young Senegalese street vendor we met in Marseille says: 'I wonder how they'll see it… because a black man who comes to donate blood… they don't look at you […]. It's an apprehension maybe, […] and already you want to do a good deed, and people look at you strangely, and finally, you wonder …' [15]. We must recognize that in many ways, access to information, the possibility of presenting identity documents during control without fear of getting into trouble, linguistic ability and citizenship are essential determinants of donation.

In summary, the donation of RBG is thus constrained, in France, by a specific configuration articulating ethical rules and, largely, situations of social, linguistic and administrative precariousness of migrant populations or those recently settled in France.

COMPARE THE INFLUENCE OF LEGAL AND ETHICAL CHOICES ON THE EFFECTIVE SUPPLY FOR RBG

In this review, we perform a reflection on the French supply system of compatible blood products for SSAA populations considering French history and its legal and cultural components. However, many Western countries are subject to the same worldwide phenomenon of population mobility and undergo blood supply issues. The decisions taken in four different countries—the United States, the Netherlands, the United Kingdom and Italy—depict an interweaving of historical, legal and ethical dimensions specific to each county and a diversity of responses to blood collection problems.

As illustrated in Table 1, these four countries encounter the same under-representation of SSAA individuals in their donor population. However, the presence of the SSAA population in these countries and their possible estimation are not subject to the same historical and social background. For example, despite descending from forced migration [50] and a history of racial segregation policies, African-Americans are demographically and statutorily constitutive of the American nation. In this country, an ethnic census with self-determination allows the possibility to know the 'racial' origin of Americans. Conversely, Italy was a country of emigration until the 1970s, and then of transit for African populations. It was only in the early 2000s that it also became a host country for immigrants from Eastern Europe, North Africa mainly, but also South Africa [51, 52]. Identification of immigrants or descendants of immigrants is based on citizenship [53]. British migration flows reflect its colonial past (i.e., significant proportion of immigration is from Commonwealth member countries and former territories of the British Empire from West Indies [Antilles], the Indian subcontinent and Africa) [54], as in France. But similar to the United States, the United Kingdom became a multicultural societal model where self-determination has indicated the ethnic origin since the 1991 census [53]. However, this approach has two limitations. First, it remains subjective and, second, the categories proposed in the census (e.g., nationality, region, subcontinent continent, skin colour) are not always standardized. In this regard, the Dutch case is interesting, which combines a recognition of its ethnic diversity to fight against discrimination, but based on the birthplace (or the birthplace of parents) and not on self-determination as in the United Kingdom [55]. The Netherlands is an example of mixed migration of Africans, on the one hand, of American origin with flows from former colonies of the Dutch Empire and, on the other hand, from recent migrations from sub-Saharan Africa for political, humanitarian or economic reasons.

Through the prism of their own historical and legal background, countries tend to conceive adapted solutions. Issues of rare blood supply are tangible in the United States, where African-Americans represent a substantial part of the needs due to RBG and a high prevalence of sickle cell disease (1/500 births) [23]. Compared to European countries, the bibliography on African-Americans blood donation is abundant and long-standing [36, 56–60]. In addition to the barriers systematically found (lack of awareness and knowledge,

TABLE 1 Overview of SSAA populations and donors and rare blood programs in France, United States, United Kingdom, Italy and the Netherlands

	SSAA individuals in general population[a]	SSAA individuals in donor population[a]	Ethnicity recognition in population [31]	RBD programs	RBD registration	Research and awareness on RBD[b]
France	4.48% of African immigrants (1.85% SSA) [5]	1.5% donors born in SSA[c]	By citizenship, birthplace and citizenship of parents for descendants of immigrants	National since 1980s (RBD database since end of 1960s) [32]	~13,000 RBD and patient registered (2016)	• National campaigns with Social Lab • Studies about determinants of blood donation with community campaigns [14–16] • University events but unspecific to SSAA • Local campaigns with territorial approach
United States	13% of Black or African-Americans [33]	3% [33]	By self-determination: decennial census with self-determined ethnicity categories	National since 1998 (RBD database since 1960s) [34]	51,000 active RBD (2013) [35]	• States campaigns • Local, religious, community campaigns [36, 37] • Studies about deferral factors [38, 39] • Studies about determinants and events on university [40]
United Kingdom	3.3% in England and Wales (Black, African, Caribbean or Black British) [41]	~1% [41]	By self-determination: decennial census with self-determined ethnicity categories and citizenship, birthplace	National program since 1952 [42]	~2000 active RBD (2016)	• Studies about determinants of blood donation for SSAA population awareness [43]: • Nationals campaigns • Local, religious, community campaigns • Communication initiative • Target events • University events
Italy	~1.6% of African immigrants (less than 1% of SSA) [44]	n/a	By citizenship: birthplace and citizenship of parents	Regional programs in Lombardy (LORD-P 2005) and Sicilia (2010) and local ones [45]	LORD-P: ~9300 RBD registered [46]	• n/a
Netherlands	3% (SSAA residents) [31]	n/a on SSAA population but only 1% from minority groups [47]	By citizenship: birthplace and citizenship of parents	National program [48] RB units frozen and stored since 1970s, Sanquin Bank of Frozen Blood since 2006	900 active RBD	• Studies about determinants of blood donation for SSAA population [18, 31, 49].

Abbreviations: n/a, not available; RB, rare blood; RBD, rare blood donor; SSA, Sub-Saharan Africa; SSAA, sub-Saharan African ancestry.

[a]As legislation differs, it refers to several options (census/estimation and nationality/ethnicity). Therefore, comparisons between them should be carefully considered. Diverse possibilities are specified.

[b]Researches about donor recruitment only (not immunohaematology aspects).

[c]Including French territories (Guadeloupe, Martinique, Guyana, Reunion island and Mayotte).

technical barriers), more sporadic obstacles include distrust of health institutions, ethnic discrimination and lack empathy due to a lack of identification with the receiver. Determinants of blood donation in the United States are well known, and further studies will enhance the accuracy of the expertise, like for European SSAA populations. But just as we cannot summarize all the variability in the perception of SSAA individuals under the umbrella of a single African culture, the representations of blood donation for African-Americans cannot be invariably applied to all other SSAA populations. In contrast to the United Kingdom, which has had a dedicated rare blood programme for over half a century [42], addressing RBG issues is new for Italy, and so is the policy for SSAA blood donation. However, despite recent attention to the issue, Italy has local programmes, plus two regional programs in Lombardy and Sicily [45]. Consequently, the country counts many active rare blood donors. Lastly, the studies of blood donation in the Dutch population of Surinamese, sub-Saharan and Caribbean ancestry have highlighted the lack of awareness and practical constraints as the main impediment [18, 31, 49]. As in France, where blood donation is possible only in French, language can be an obstacle in the Netherlands because it is done only in English or Dutch. The Netherlands still has only a few SSAA donors compared to the general donor population. As it happens in other countries, importation of compatible blood for African blood phenotypes is required, and therefore European and international collaboration is indispensable.

At the European scale, the European Blood Alliance initiated the Missing Minorities (MIMI) project to understand low donation determinants among minorities in Europe. It demonstrates the increased awareness of European countries regarding blood donation by people of African ancestry. However, government-wide management of rare blood remains at an early stage [47]. All the studies recently conducted at the European level highlight the relevance of this topic [61]. Ultimately, blood drive policies are different. It appears that their definitions are probably more influenced by their socio-political histories and ethical choices rather than by technical and medical considerations alone. This multidisciplinary approach is essential and has resulted in concrete actions.

EFS SOCIAL LAB: A FRENCH INTENT TO IMPROVE BLOOD SUPPLY OF SSAA POPULATIONS

Although legislation evolves to suit societies and their needs, it is unlikely that the limitations regarding the ethnic origins of individuals will change soon in France, restricting leeway for anticipating needs. Current socio-political debates on blood donation mainly concern blood donation at 17 years of age or the restrictions for men who have sex with men. Despite this, it is still possible to work on new donor recruitment.

In 2018, the EFS created an internal working group called 'EFS Social Lab', made up of around 15 EFS professionals (e.g., MD, communicators, researchers). EFS Social Lab monitors the donors and societal trends to identify topics that may impact blood donation (e.g., the donor recognition in a voluntary blood donation system, the conversion from whole-blood donation to plasma donation, the evolution of commitments among young people, and, as we have just described, blood donation in minorities). The final objective is to give recommendations based on evidence and not just perceptions to guide the EFS executive direction in strategic decision making.

On this basis, the work began with a bibliographic inventory supplemented by surveys, as well as masters and PhD studies in connection with the academic world. Three organizational deficiencies stood out: the insufficient and non-procedural orientation of the recipients and their siblings to donation, the non-specific collection policy and donor relationship, and a welcome system insufficiently attentive to diversity. The EFS Social Lab made recommendations based on 10 points.

To optimize the existing system and define a specific programme for rare blood:

1. Review current procedures, check their range of application and identify their weaknesses.
2. Review the current collection practices for recruiting rare donors (RDs).
3. Define RBG donors and proceed with adequate information depending on the frequency of the phenotype in the population.
4. Define a specific donor care.

To create a network of rare blood referents including doctors from the blood collect:

5. Identify one or several 'rare blood' referents in each regional blood transfusion centre.
6. Produce an annual activity report for each regional blood centre.
7. Create a dynamic network of rare blood referents based on sharing and feedback.

To evaluate the efficiency of recruitment actions:

8. Define a methodology and a protocol to apply to guarantee the validation of the effectiveness of the actions.

To help recruit rare blood donors for blood drive managers:

9. Create a reference tool to help them identify the places to collect and the validated recruitment actions to implement.

To train EFS employees and partner volunteers:

10. Create specific training at a national level.

WHICH SOCIAL APPROACH TO BLOOD DONATION?

For some socio-political spaces, blood is a marketable product. For others, it has a human and non-mercantile value that cannot be

indexed to a price. It also expresses how much giving blood reflects the symbolic representations of oneself, inherent in identity, transmission and filiation. It refers to the sedimentation of the memory of events in which blood was brought to the fore: the contaminated blood affair, the mad cow disease and HIV. Finally, it shows how much the act of giving is part of an expectation of recognition, not necessarily pecuniary, but identity-related.

Indeed, the willingness to donate inscribes the donor in a social community, and if accepted, the donation confirms membership to this community. And this is probably why sexual or territorial minorities are fighting for a right to give, which is synonymous with a confirmation of legitimate social existence. 'The idea that the gift must be returned presupposes that the other is another self that must act like me, and this gesture in return must confirm to me the truth of my gesture, that is, my subjectivity [...], men confirming to one another that they are not things' [62].

But donor recruitment requires the aptitude to mobilize citizens living in evolving societies where social consideration stands above in a multicultural and diverse globalized world. The crucial achievement is to translate academic and practical knowledge into concrete and successful actions. Research and action must be conducted simultaneously and over the long term. It is important to involve the collection operators as early as possible in the development of the experimentation protocols. This is the only way to ensure their future integration into operational procedures for long-term effectiveness. We are increasingly using the human and social sciences to understand the motives of social actors, to dialogue with various populations and to improve the quality of relations with donors at blood drives. However, although they have proven to be effective, these actions aimed at better understanding the contexts of our medical actions are difficult to sustain, as in the case of our anthropological study [14]. We consider, however, that an institutional policy is necessary to patiently build social and health interfaces that will allow us to improve the recruitment problems of the SSAA populations.

We cannot go any further in the framework of a brief exploratory review but merely underline that ensuring the functional chain of blood from the evaluation of needs to the setting up of an alert system, the availability of blood products, and the coherent use of rare bloods requires the construction of an epistemological and technical interdisciplinary space between medical and social sciences.

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CONFLICT OF INTEREST

The authors declare no conflict of interests.

ORCID

Pauline Oviedo https://orcid.org/0000-0002-3654-6406
Jacques Chiaroni https://orcid.org/0000-0002-3133-8990

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ORIGINAL ARTICLE

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Blood donation behaviour and attitudes towards the 12-month deferral policy among gay and bisexual men in New Zealand

Koson Tony Sriamporn[1] | Peter Saxton[1] | Nathan Consedine[2] | Mohamed Hammoud[3] | Garrett Prestage[3]

[1]School of Population Health, University of Auckland, Auckland, New Zealand

[2]School of Medicine, University of Auckland, Auckland, New Zealand

[3]Kirby Institute, University of New South Wales, Sydney, New South Wales, Australia

Correspondence
Koson Tony Sriamporn, School of Population Health, University of Auckland, Grafton Campus, Auckland 1023, New Zealand.
Email: tony.sriamporn@auckland.ac.nz

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Abstract

Background and Objectives: Gay and bisexual men (GBM) are deferred from donating blood in many countries. Perceptions by GBM that blood donor deferral policies are unjustifiably discriminatory, especially due to advances in HIV prevention, could contribute to non-compliance and need to be understood. We explore blood donation interest and history among GBM and attitudes towards donor deferral policies for the first time in New Zealand (NZ).

Materials and Methods: Data from a cross-sectional online survey of GBM in NZ were examined. We constructed three groups: (1) never donated blood and not interested; (2) never donated but expressed interest; and (3) previously donated blood. We tested these for association with demographic and behavioural variables, as well as attitudes towards blood donation policy.

Results: A total of 607 GBM were eligible for the study, of whom 32.9% reported having donated blood previously, 44.3% had never donated blood but expressed interest and 22.7% expressed no interest in donating. Among previous donors, a third (8.6% of the total sample) reported non-compliance with the deferral policy. Most participants found the 12-month deferral policy to be too strict (81.8%), unfair (75.4%) and homophobic (68.8%).

Conclusion: We estimate that, for the first time in NZ, almost 10% of the sample did not report compliance with the 12-month deferral policy for men who have sex with men (MSM). Negative attitudes towards the deferral policy were common and could potentially increase the risk to the blood supply if compliance reduces. Further work is needed to inform a deferral policy that is accepted by GBM while maintaining the safety of NZ's blood supply.

Keywords

attitudes, blood donation, blood safety, deferral policy, donors, men who have sex with men

Highlights

- Blood donation behaviour, compliance, interest and attitudes among gay and bisexual men in New Zealand were similar to existing studies in other populations.

- Although negative attitudes were widespread, two-thirds of our sample complied with policy by not donating blood.
- Perceived injustices may contribute to non-compliance; ongoing efforts are needed to make the policy more inclusive while maintaining the safety of the blood supply.

INTRODUCTION

It remains a global challenge to formulate a blood donor deferral policy that maintains a safe blood supply while simultaneously minimizing bias on groups affected by the policy. In response to the growing pandemic of acquired immunodeficiency syndrome (AIDS) in the early 1980s, many countries restricted blood donations from groups at higher risk, including men who have sex with men (MSM). This precautionary approach to donation was necessary, at the time, to protect transfusion recipients against blood-borne transfusion transmissible infections (TTI) in the absence of testing that could detect the human immunodeficiency virus (HIV). However, these deferral policies have remained in place even as HIV testing technology has improved. MSM have criticized the policies as unnecessarily discriminatory, advocating that they be reduced or removed entirely.

The effectiveness of deferral policies in maintaining the safety, and the perceived safety of the blood supply, is determined by the level of non-compliance (i.e., donating despite being ineligible under deferral criteria). Although all types of donated blood are tested, there is a small but not zero chance that a non-compliant individual with an unrecognized incident TTI will donate, the infection will not be detected, and the blood will subsequently be transfused [1]. Additionally, for various reasons donors may withhold information about high-risk behaviours that would preclude donation. For example, in an interview with 272 Dutch repeat donors with confirmed TTI, 76 donors admitted to not complying with the deferral policy, mostly because of male-to-male sexual contact [2]. Non-compliance creates avoidable risks to the blood supply and to blood recipients [3–5]; these reasons should be explored in each policy setting.

Studies into MSM donor attitudes provide insight into why non-compliance might occur. In previous studies, MSM who donated blood in spite of being ineligible cited the unfairness of the exclusion as a reason to not self-defer [4, 6]. Other data suggest that non-compliant individuals did not want to disclose MSM behaviour at the point of donation [7, 8] and that they viewed their sexual behaviours as low-risk for HIV [1, 4]. Similarly, most of an Australian sample of MSM regarded that country's 12-month deferral policy to be 'unfair', 'homophobic' and 'too strict' given that most MSM adopted effective HIV prevention strategies [9]. Because of the cultural and behavioural differences across countries, MSM's negative attitudes towards the blood donor policy should be understood within each country's policy setting.

Contemporary blood donor deferral policies for MSM vary globally, as agencies attempt to reflect modern HIV testing methods, local HIV epidemiology and contemporary HIV prevention practices while allowing MSM to fairly participate in blood donation. Despite the current ability of proprietary laboratory-based nucleic acid testing to reliably detect an incident HIV infection acquired after 2 weeks [10], a few countries still indefinitely exclude MSM from donating blood [11]. Other countries, like New Zealand (NZ), use time-based deferrals since prospective donors' reported last episode of oral or anal intercourse between men, ranging from 10 years to 3 months [11]. Recently, the United Kingdom adopted one of the least restrictive policies for MSM, where gender-neutral behavioural risk assessments are undertaken [12].

Little is known about donation attitudes in NZ. Like many countries, NZ has progressively reduced the time-based deferral for MSM, following evidence that such reductions would not increase the risk to recipients. In 2014, the NZ Blood Service (NZBS) convened an independent expert review of the deferral criteria based on sexual behaviours [13], resulting in a policy liberalization for MSM (a reduction from the 5-year deferral period to a 12-month deferral). The review considered but did not recommend removing oral sex (which carries a zero to the negligible risk of HIV transmission) as grounds for MSM deferral. It did, however, recommend that research be conducted among MSM to explore attitudes towards NZ's 12-month deferral policy to gain insight into likely compliance [13]. In the intervening years, the NZBS policy has continued to garner negative attention from MSM [13, 14], but despite this, no relevant research is available.

Our paper addresses this evidence gap by descriptively characterizing the past behaviours (including possible compliance), attitudes and intentions of NZ MSM regarding NZBS's 12-month blood donor deferral policy (spanning from 2015 to 2020) in a large national cross-sectional sample.

MATERIALS AND METHODS

Design

The Following Lives Undergoing Change (Flux) NZ Study is a confidential, online, national, cross-sectional survey that was adapted from the Australian Flux Study in partnership with the Kirby Institute at the University of New South Wales. Participants were recruited between December 2018 and February 2019 through social media, gay mobile applications, community organizations and in person at a community fair day in Auckland. To be eligible, participants had to be at least 16 years old, have had sex with another man in the last 6 months or identify as gay, bisexual or non-heterosexual. Consent was obtained before being sent a link to a questionnaire that was hosted online. No monetary compensation was offered for participation. The study was approved by the University of Auckland Human Participant Ethics Committee (#020977).

Participants

During the study period, people living with HIV or who have ever injected non-prescription drugs were permanently deferred from donating blood in NZ and were therefore excluded from analyses. Participants were also excluded if they did not provide a response to the question 'Have you previously donated blood?' To note, when referencing behaviour and policy, we refer to the population as MSM. However, when discussing the impact on the community, we refer to gay, bisexual and other MSM Gay and bisexual men (GBM).

Measures

Items included basic demographics and questions regarding their sexual identity, self-reported HIV status and pre-exposure prophylaxis use. Age was simplified into three categories, under 30, between 31 and 45, and over 45. Education was measured as a binary variable: those with and those without a University degree. Participants were able to report multiple ethnicities as per standard NZ Census practices; these responses were recoded into six single levels according to the following hierarchical order [15]: Māori, Pacific, Asian, Middle Eastern, Latin American or African, Other, then NZ European.

MSM self-reported risk and testing behaviours in the last 6 months relevant to the recent UK FAIR blood recommendations [16]; these responses were dichotomised (yes/no). MSM also reported recent HIV and sexually transmitted infection (STI) testing behaviour and any STI diagnoses in the last 6 months.

Questions surrounding attitudes and intentions towards blood donation and deferral policies were taken from the Australian FLUX Study [9] with no further adaptations for the NZ setting. At the time, both the NZ and Australian deferral for MSM were set at 12 months. Participants were asked to rate how much they agreed with eight statements on a 6-point Likert scale (1 = strongly disagree to 6 = strongly agree). Participants were also asked about their awareness of the blood donor deferral policy, and previous donors were asked, 'did you have anal or oral sex with another man 12-months prior to donating' to measure compliance.

Analysis

Data were analysed using IBM SPSS Statistics 27 (IBM Corp). Participants were stratified into three discrete blood donation status groups: (1) Never donated blood and not interested, (2) never donated but expressed interest, and (3) previously donated blood. All categorical variables were described using basic frequencies and proportions, then a test for independence between donation status groups was assessed using Pearson's χ^2 test for independence and p-values were reported for significant differences in proportions. Four blood donation attitudinal and four intention items were split into two categories, and responses 1–3 were recoded as 'agree' and 4–6 were recoded as 'disagree' to describe the overall response proportion. Further, we used a series of one-way analyses of variance tests to investigate significant differences between blood donation status groups in their responses to the attitudinal and intention items, and post hoc comparisons were conducted for each significant model. Type I errors of 5% with Bonferroni corrections were used for all analyses.

RESULTS

Figure 1 shows the flow chart of the 836 MSM who completed the FLUX questionnaire into the final sample of 607 MSM. Two-thirds of this sample (67.5%) had not donated blood before. Among those who had never donated, 64.7% expressed interest in donating blood in the

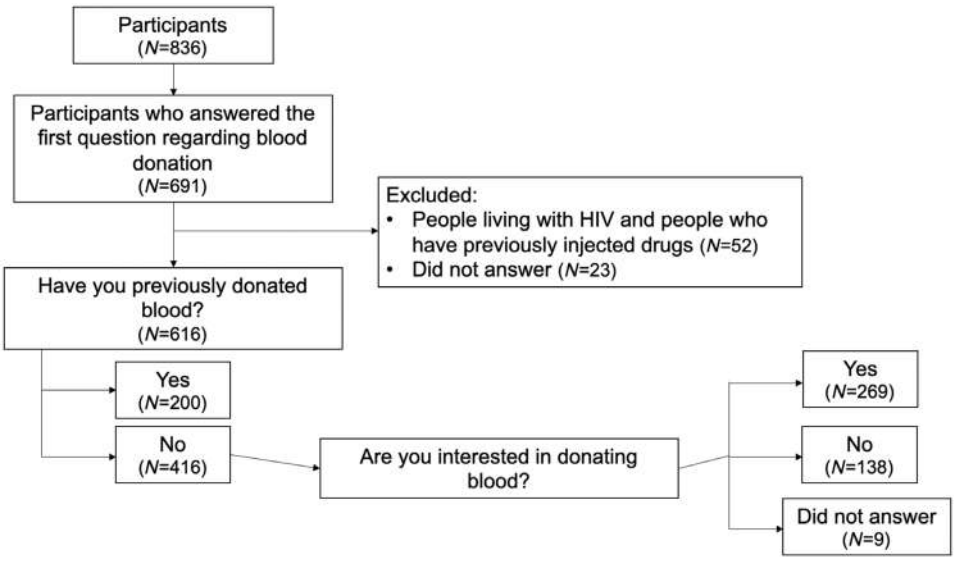

FIGURE 1 Participant flow diagram

TABLE 1 Sample characteristics, history of blood donation and interest in donation

Variables	Never donated, not interested (%)	Never donated, interested (%)	Previously donated (%)	Total sample (%)	χ^2(df), *p*-value
	138 (22.7)	269 (44.3)	200 (32.9)	607 (100)	
Age					
<30	57 (41.3)	153 (56.9)[a]	88 (44.0)	298 (49.1)	23.05 (4), <0.001
31–45	39 (28.3)	82 (30.5)	61 (30.5)	182 (30.0)	
45<	42 (30.4)	34 (12.6)[a]	51 (25.5)	127 (20.9)	
Education					
No University degree	58 (42.0)	155 (57.6)[a]	89 (44.5)	302 (49.8)	12.16 (2), 0.002
University degree	80 (58.0)	114 (42.4)[a]	111 (55.5)	305 (50.2)	
Employment					
Employed full-time	83 (60.1)	155 (58.1)	136 (68.3)	374 (61.9)	12.39 (6), 0.054
Employed part-time	15 (10.9)	28 (10.5)	14 (7.0)	57 (9.4)	
Student	20 (14.5)	61 (22.8)	34 (17.1)	115 (19.0)	
Other	20 (14.5)	23 (8.6)	15 (7.5)	58 (9.6)	
Ethnicity					
NZ European	105 (76.1)	207 (77.0)	151 (76.3)	463 (76.5)	11.81 (10). 0.298
Maori	14 (10.1)	26 (9.7)	22 (11.1)	62 (10.2)	
Pacific	0 (0.0)	8 (3.0)	9 (4.5)	17 (2.8)	
Asian	14 (10.1)	16 (5.9)	10 (5.1)	40 (6.6)	
MELAA	4 (2.9)	6 (2.2)	3 (1.5)	13 (2.1)	
Other	1 (0.7)	6 (2.2)	3 (1.5)	10 (1.7)	
HIV status					
HIV positive	*Excluded*				
HIV Neg, PrEP	29 (21.0)	51 (19.0)	39 (19.5)	119 (19.6)	5.17 (4), 0.271
HIV Neg, no PrEP	84 (60.9)	159 (59.1)	133 (66.5)	376 (61.6)	
Never tested/unknown	25 (18.1)	59 (21.9)	28 (14.0)	112 (18.5)	
Identity					
Gay	107 (77.5)	214 (79.6)	155 (77.5)	476 (78.4)	0.37 (2), 0.832
Bisexual/others	31 (22.5)	55 (20.4)	45 (22.5)	131 (21.6)	

Note: Some cells may not equal 100% due to missing data.
[a]Significant differences from expected cell value ($p < 0.05$ with Bonferroni corrections).

future (44.3% overall), 33.2% were not interested (22.7% overall), and the remaining 2.1% ($N = 9$) participants were excluded from analyses as they did not provide a response.

Table 1 shows the demographic characteristics of participants according to their blood donation status. The mean age was 34.2 years old (SD = 14.2). Post hoc comparisons between donation status groups showed a higher proportion of MSM under 30 who were interested in donating but had never done so (56.9%; $p = 0.020$). We also found a lower proportion of MSM aged over 45 years old who were interested in donating compared to the other age groups (12.6%; $p < 0.001$) and a higher proportion of those without a University degree who expressed interest in donating blood in the future (57.6%; $p = 0.003$).

A third of the participants (32.5%) had donated blood. Table 2 summarizes the last time participants donated blood, most (28.5%) during 2015–2020 when deferral was 12 months. Of these previous donors, 53 (8.7% of the sample population) reported having had anal or oral sex with another man within the 12 months before donating blood, 140 had not and the remaining 7 did not answer.

TABLE 2 Previous donors' latest donation event stratified by deferral period

Year	NZBS deferral period	Total (%)
Before 1983	N/A[a]	9 (4.5)
1984–1998	N/A[b]	40 (20.0)
1999–2008	10 years	47 (23.5)
2009–2014	5 years	44 (22.0)
2015–2020	12 months	57 (28.5)
Did not answer		3 (1.5)

[a]Before NZ's first AIDS diagnosis in 1983.
[b]No deferral times were set before NZBS was established in 1999. However, MSM were asked to not donate blood. This practice may have varied by regional services.

TABLE 3 Risk and testing behaviours in the last 6 months

Variables	Never donated, not interested (%)	Never donated, interested (%)	Previously donated (%)	Total sample (%)	χ^2(df), *p*-value
Number of sexual partners					
0	20 (14.5)	36 (13.4)	29 (14.5)	85 (14.0)	0.46 (4), 0.978
1	31 (22.5)	67 (24.9)	46 (23.0)	144 (23.7)	
2+	87 (63.0)	166 (61.7)	125 (62.5)	378 (62.3)	
Exchanged money for sex					
Yes	18 (13.0)	34 (12.7)	19 (9.5)	71 (11.7)	1.45 (2), 0.484
No	120 (87.0)	233 (87.3)	181 (90.5)	534 (88.3)	
Tested for STI					
Yes	81 (58.7)	153 (56.9)	110 (55.0)	344 (56.7)	0.46 (2), 0.794
No	57 (41.3)	116 (43.1)	90 (45.0)	263 (43.3)	
STI diagnosis					
Yes	19 (14.0)	39 (14.5)	25 (12.8)	83 (13.8)	0.29 (2), 0.864
No	117 (86.0)	230 (85.5)	171 (87.2)	518 (86.2)	
Non-injecting recreational drug use					
Yes	70 (50.7)	161 (60.3)	115 (57.8)	364 (57.3)	3.44 (2), 0.179
No	68 (49.3)	106 (39.7)	84 (42.2)	258 (42.7)	

Note: Cells may not add up to $N = 607$ due to missing data.

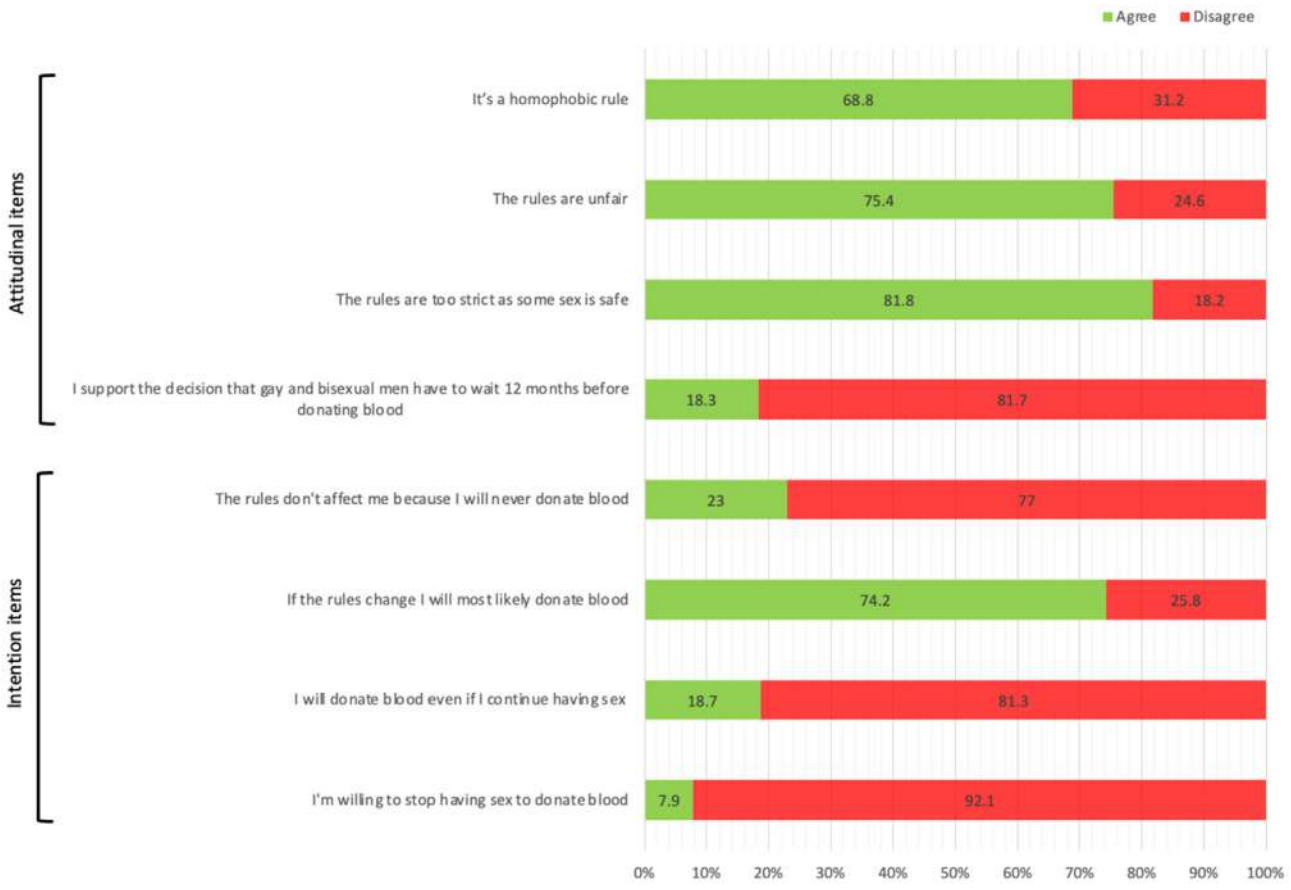

FIGURE 2 Proportion of the total MSM population who agree/disagree

TABLE 4 Mean and SD responses to attitudes towards blood donation policy in 2019

Variables	Never donated, not interested (NN)	Never donated, interested (NI)	Previously donated (PD)	Total sample	*F*(df), *p*-value	Post hoc comparisons
Attitudinal items						
It is a homophobic rule.	3.93 (1.8)	4.43 (1.7)	4.06 (1.8)	4.19 (1.8)	4.59 (2597), 0.011	NN < NI*
The rules are unfair.	4.10 (1.7)	4.76 (1.6)	4.43 (1.7)	4.51 (1.7)	7.40 (2595), 0.001	NN < NI*
The rules are too strict as some sex is safe.	4.17 (1.6)	4.85 (1.4)	4.69 (1.5)	4.65 (1.5)	9.21 (2595), <0.001	NN < NI*, PD**
I support the decision that gay and bisexual men have to wait 12 months before donating blood.	2.71 (1.7)	1.84 (1.3)	2.21 (1.6)	2.15 (1.5)	15.47 (2598), <0.001	NN > NI**, PD*; NI < PD*
Intention items						
The rules do not affect me because I will never donate blood.	4.38 (1.5)	1.70 (1.1)	1.77 (1.3)	2.32 (1.7)	217.77 (2588), <0.001	NN > NI**, PD**
If the rules change I will most likely donate blood.	2.51 (1.4)	5.07 (1.3)	4.89 (1.6)	4.44 (1.8)	157.66 (2593), <0.001	NN < NI**, PD**
I will donate blood even if I continue having sex.	1.89 (1.3)	2.22 (1.6)	2.15 (1.6)	2.12 (1.6)	2.10 (2595), 0.123	*ns*
I am willing to stop having sex to donate blood.	1.45 (0.9)	1.69 (1.2)	1.65 (1.2)	1.62 (1.1)	2.19 (2591), 0.112	*ns*

Note: Mean (SD). ANOVA with Bonferroni corrections was conducted for mean differences between groups. *$p < 0.05$; **$p < 0.001$. Measured on a 1–6 Likert scale (1 = strongly disagree, 6 = strongly agree).

Overall, the prevalence of risk and testing behaviours in the past 6 months did not significantly differ between the three blood donation status groups (Table 3).

Blood donation

Most (83.8%) of those who had previously donated reported awareness of the blood deferral policy, which was not significantly different to those who had never donated but expressed interested (82.5%) and not interested in donating (77.2%; $F(2) = 2.50$, $p = 0.287$).

Attitudinal items

Figure 2 shows the proportions of MSM who agreed and disagreed with each of the items. A high proportion of our overall sample viewed the rules to be 'unfair' (75.4%) and 'homophobic' (68.8%). Around four in five MSM did not support the 12-month deferral period in place at the time of the study (81.7%) and believed these rules to be 'too strict' as some sexual activities are safe (81.8%). Post hoc tests (Table 4) revealed that interested non-donors were least supportive of the policy (*p*s < 0.026), and consistently held significantly more negative attitudes (*p*s < 0.022) compared to non-interested non-donors. In comparison to other groups, non-donating MSM, who showed no interest in donating, viewed the deferral rules to be the least strict (*p*s < 0.008).

Intention items

Three-quarters (77.0%) of the sample believed that the rules affected them because they will donate blood in the future, with non-interested non-donors indicating that the rules would impact them the least compared to the other two groups (*p*s < 0.001). Overall, 74.2% of all MSM would donate in the future if the rules changed, but post hoc tests showed that the responses were the strongest among interested donors ($p < 0.001$) and previous donors ($p < 0.001$) when compared to non-interested MSM who had never donated. Despite low support for the deferral policy, the majority would not donate blood if they continued to have sex (81.3%). However, most of our sample (92.1%) were not willing to stop having sex with other men in order to donate blood.

DISCUSSION

We show for the first time in NZ that a third of MSM surveyed have donated blood at least once in their lifetime. A third of previous donors, comprising 8.6% of the total sample, reported that they had sex with another man 12 months before donating blood; that is, apparent non-compliance with the deferral policy. Among the non-donors, two-thirds reported interest in donating blood in the future.

Overall, despite high levels of negative attitudes reported across our three donation status groups, two-thirds of the sample did not donate blood and reported compliance with the policy.

A strength of our data is that it was collected from a study that was promoted as research on HIV risk behaviours among MSM, not blood donation. This may have minimized study participation biases and provided a more accurate estimate of MSM's attitudes towards blood donation. The self-reported online survey completion mode may have a limited bias in social desirability responding as blood donation is seen as a desirable act [17] among MSM [18]. Although the Flux NZ study of higher risk MSM samples (half of our sample reported recreational drug use and a tenth exchanged money for sex), their engagement in contemporary HIV prevention and gay social practices means they are of interest to blood donation policymakers.

Limitations include the data being self-reported. We cannot verify previous donations, nor did we follow up with previous donors to request more information about past donations. At the time, the deferral period was set at 12 months for MSM. We could be underreporting the level of non-compliance due to the phrasing of the question, especially for those who donated before 2014 (when the deferral period was reduced from 5 years to 12 months in NZ), as we only asked about sex between men for up to 12 months before donating. Our participants are a self-selected national online sample, limiting the generalizability of our findings. For example, we had fewer participants who identified as Māori or Asian compared to the 2018 Census.

The prevalence of lifetime MSM donors is consistent with studies conducted in countries with similar donation deferral policies for MSM. For example, 28.5% of MSM in Australia [9] and 23% from San Francisco had previously donated blood [19], but our estimate (32.5%) is lower than the estimate of 45% of MSM in New Orleans and 38.9% in Chicago [20]. Additionally, 44% of our non-donors reported interest in donating blood, but this is in the lower range of 48%–92% [8, 9, 19–21] compared to other countries. The lower proportion in our sample is most likely due to methodological differences, as we only posed the question about interest in donating to those who had not donated before. We expect that there are a number of previous donors who also would be interested in donating blood as previous donations are the best predictor of future donations [22]. Regardless, we have shown for the first time that a high proportion of NZ GBM is interested in, and some have donated blood, in spite of deferral policies, which excluded most GBM.

Although the prevalence of the previous donation is similar to other countries, these findings are concerning as many MSM in NZ would be ineligible to donate. For example, repeat HIV prevention surveys show that most (>90%) NZ GBM report male-to-male sexual contact in the previous 6 months [23]. It is also possible that there are some participants who interpreted a 'blood donation' to be a standard laboratory blood test, as the term was not defined in the questionnaire. We must treat these as preliminary findings until we can support the results with studies that differ in validation methodologies (e.g., longitudinal studies or partnering with the blood service to confirm donations). Nevertheless, these novel findings suggest that there are MSM donating blood despite being potentially ineligible in NZ, further highlighting the need to address the aspects of NZ's deferral policy that may not be supported by MSM.

The level of self-reported non-compliance found in our sample is comparable to the United Kingdom. Comparing non-compliance within a general MSM sample, a 2011 UK report found that 10.6% of all MSM (vs. 8.6% in our study) had donated blood during the period with a lifetime ban [6]. When comparing non-compliance within MSM donors, 28.6% non-compliance in our sample is similar to another 2015 UK report, which estimated non-compliance within MSM donors at 30.6% [24]. However, we note that our estimate of non-compliance is lower than 18.3% previously reported in a French study [4], which used an anonymous post-donation design. Although this is likely due to differences in the sampling method (our study did not target confirmed donors), any level of non-compliance among MSM remains a concern for the safety of NZ's blood supply.

Consistent with the literature [9, 25], many MSM in our sample expressed their willingness to donate if the donor criteria changed. The desire to donate was much stronger among those who had previously donated and non-donors who expressed interest. This was expected as the biggest predictor of a future blood donation is having donated previously [26]. Our results are the first to show that there is high interest and willingness in blood donation participation among MSM in NZ. However, it is unlikely that all these individuals will register as a donor in the future, as the willingness to perform a behaviour does not perfectly translate to actual behaviour [27].

Our findings suggest that negative attitudes towards the donor deferral policy are widespread among MSM. Consistent with Clackett and colleagues' study [9], these negative attitudes were reflected among non-donors and especially among non-donors who expressed interest in donating. These results were unsurprising among previous donors, as it is well documented that the perceived unfairness and discrimination is one of several reasons for donating blood among MSM who were confirmed to be non-compliant [4, 6, 24]. One explanation for negative attitudes towards the policy may be due to the ongoing inclusion of oral sex among the deferrable behaviours, despite the general scientific consensus that oral sex poses little to no risk of transmitting HIV [28]. MSM may reasonably believe that oral sex is considered 'safe,' but they remain deferred. Future studies should investigate factors that may determine whether a prospective MSM will comply with the policy (e.g., self-defer) or donate in spite of ineligibility.

In conclusion, our study is the first to report on the attitudes MSM have towards the 12-month blood donor deferral policy in NZ. This adds to the published evidence that some MSM donate blood despite their ineligibility. The findings also indicate that, while there is a significant willingness and interest in donating blood among the community, many MSM did not support and held negative attitudes towards the policy. We suggest that the perceived moral injustice towards the community may contribute to the high levels of non-compliance, and as such, poses an avoidable risk to the blood supply. We recommend continued efforts to widen blood donation opportunities for MSM while keeping the blood supply safe. We also suggest ongoing communication with MSM communities to bridge possible misunderstandings and resentment towards the blood service. Doing so may limit levels of

non-compliance and the impact that may have on the safety of the blood supply.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ORCID

Koson Tony Sriamporn https://orcid.org/0000-0003-1027-5182

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ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

Efficacy, safety and pharmacokinetics of a new 10% normal human immunoglobulin for intravenous infusion, BT595, in children and adults with primary immunodeficiency disease

Gergely Kriván[1] | Michael Borte[2] | James B. Harris[3] | William R. Lumry[4] | Silke Aigner[5] | Stephan Lentze[5] | Christiane Staiger[5]

[1]Department of Pediatric Hematology and Stem Cell Transplantation, Central Hospital of Southern Pest - National Institute of Hematology and Infectious Diseases, Budapest, Hungary

[2]ImmunDeficiencyCenter Leipzig (IDCL) at Klinikum St. Georg gGmbH, Leipzig, Germany

[3]The South Bend Clinic, South Bend, Indiana, USA

[4]AARA Research Center, Dallas, Texas, USA

[5]Biotest AG, Dreieich, Germany

Correspondence
Christiane Staiger, Biotest AG, Landsteinerstr. 5, Dreieich, Germany.
Email: christiane.staiger@biotest.com

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Abstract

Background and Objectives: To evaluate the efficacy, safety and pharmacokinetics of a new, highly purified 10% IVIg (BT595, Yimmugo®) administered in children and adults with Primary immunodeficiency diseases (PID).

Materials and Methods: Prospective, uncontrolled, multicentre Phase III trial. Patients aged 2 to <76 years with PID were switched from their pre-trial IVIg replacement therapy to BT595. In all, 67 patients (49 adults, 18 children) received doses between 0.2 and 0.8 g/kg body weight for approximately 12 months at intervals of 3 or 4 weeks. Dosing and dosing intervals were based on each patient's pre-trial infusion schedule. The primary end point was the rate of acute serious bacterial infections (SBIs); secondary efficacy, safety and pharmacokinetic outcomes were also evaluated.

Results: The primary efficacy end point was met, and the unadjusted SBI rate was 0.01 per subject-year (adjusted SBI rate 0.015 per subject-year, with an upper limit of the one-sided 99% confidence interval of 0.151). A single adult patient experienced one event classified as an SBI. All secondary end points, including those related to infections, supported the efficacy. Infusion rates were increased up to 8 ml/kg/h. Overall, 8% of infusions were associated with ≥1 infusional adverse event (AE) (start during or within 72 h post-infusion), comprising mainly headache (2.4%), fatigue (0.9%) and nausea (0.5%). There were no infusional AEs at infusion rates of >4.0 ml/kg/h, and only one patient required a single premedication. The observed patterns, severity and frequency of treatment-emergent adverse events are consistent with the established safety profile for IVIgs and did not show clinically relevant differences between all age groups.

Conclusion: BT595 is effective, safe and well tolerated for treating patients with PID.

Keywords

efficacy, pharmacokinetics, PID, safety, tolerability

Highlights

- The results of this pivotal Phase III trial demonstrate that BT595 is highly effective and safe as a replacement therapy in patients with primary immunodeficiency disease for preventing infections.
- The outcomes of the secondary end points were consistent and supported the efficacy and safety of BT595 in all age groups.
- BT595 demonstrated pharmacokinetic (PK) properties in line with the well-characterized PK profiles of other licensed intravenous immunoglobulin products.

INTRODUCTION

Primary immunodeficiency diseases (PIDs) are a class of genetic disorders characterized by a defect in the human immune system. PID affects approximately 1%–2% of the worldwide population [1], with X-linked agammaglobulinaemia and Common Variable Immunodeficiency being the main antibody deficiency syndromes of clinical significance. These disorders are marked by hypogammaglobulinaemia and defective antibody production. Children and adults with PID are at an increased risk of recurrent infections, particularly respiratory tract infections. A mainstay of treatment for PID is regular replacement therapy with immunoglobulins. The provided antibodies help to prevent viral and bacterial diseases in patients with primary or secondary immune deficiencies and recurrent infections [2–6]. It is now understood that sufficient trough levels improve patients' well-being.

BT595 (Yimmugo®, a registered trademark in the European Union and certain other countries, Biotest AG, Dreieich, Germany) is a highly purified, new 10% preparation of normal human immunoglobulin for intravenous administration (IVIg) and shows the full functionality expected of an IVIg product while maintaining the physiological IgG subclass distribution. The manufacturing process comprises four effective virus inactivation/removal steps (i.e., caprylic acid treatment, pH 4 treatment, anion exchange chromatography and 20 nm nanofiltration), resulting in high margins of safety with respect to infectious viruses. In addition, low levels for IgA, IgM and accompanying plasma proteins are also achieved, and the drug product has been shown to have no procoagulant activity [7].

Here, we report the results of a clinical trial with BT595 in paediatric and adult patients with PID.

METHODS

The trial was conducted in accordance with the International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines and the Declaration of Helsinki. The trial protocol and all other relevant documents were reviewed and approved by the competent local Independent Ethics Committees. Written informed consent was obtained from all patients or patients' parents/legal guardians.

Trial product

BT595 was manufactured by using plasma from healthy donors from selected European countries and the United States. The extraction of the IgG from the pooled plasma was performed by fractionated cold/ethanol precipitation, a method originally developed by Cohn, followed by an ion exchange chromatography and other downstream purification steps, including the removal of potentially contaminating viruses, while achieving high purity and low content of polymers and dimers. The final sugar-free, glycine-stabilized product of BT595 contains 100 g of human plasma protein per litre (i.e., 10% solution). The distribution of IgG subclasses is approx. 62% IgG1, 32% IgG2, 4% IgG3 and 1%–2% IgG4. The IgA content is limited to ≤0.5 mg/ml.

Trial design

This was an open-label, prospective, uncontrolled, multicentre Phase III pivotal trial to assess the efficacy, safety and pharmacokinetics (PK) of BT595 in paediatric and adult patients with PID (EudraCT: 2015-003652-52/17046; NCT02810444).

The primary objective was to demonstrate that the rate of acute serious bacterial infections (i.e., the mean number of acute serious bacterial infections [SBIs] per subject-year) was less than 1.0 to provide substantial evidence of efficacy. Specific diagnostic criteria for SBIs were used as per Food and Drug Administration (FDA) guidance, that is, bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia and visceral abscess. This included any adverse event (AE) leading to the following Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs): sepsis, bacterial sepsis, bacteremia, meningitis bacterial, osteomyelitis bacterial, arthritis bacterial, pneumonia bacterial and abdominal abscess [8]. Furthermore, all AEs leading to any other PT were reviewed by the sponsor for a possible relationship to the primary end point (e.g., AEs, including one of the following words: bacteremia, sepsis, meningitis, osteomyelitis, arthritis, pneumonia and abscess). Identified AEs possibly related to the primary end point were queried to the investigator to clarify if the AE fulfilled the FDA-defined SBI criteria. Any SBI had to be confirmed by objective findings (e.g., X-ray, laboratory data).

The secondary objectives of this trial, in addition to further efficacy assessments, were to assess the safety and PK characteristics of BT595. Changes in health-related quality of life (HR-QoL) were added

to the protocol following advice received from the FDA and considered as exploratory end points.

Patients and treatment

Male or female patients aged 2 to <76 years were eligible for participation if they had a diagnosis of PID with impaired antibody production, that is, common variable immunodeficiency (CVID) or XLA, as defined by the diagnostic criteria of the European Society for Immunodeficiencies (ESID) and the Pan American Group for Immunodeficiency (PAGID) [9, 10].

Further inclusion criteria were stable IVIg therapy with any IVIg reference preparation during the previous 6 months, and with a single preparation for ≥3 months at either a 3-week (Q3W) or 4-week (Q4W) schedule with a constant IVIg dose that did not change by ±20% of the mean dose, regular dosage intervals, and at least one IgG trough level of ≥5 g/L during the previous 3 months.

Exclusion criteria included a history of thrombotic events within the 6 months before the start of treatment with BT595 or the presence of significant risk factors for thrombotic events, therapy with live-attenuated virus vaccines within 3 months before start of the trial, a known intolerance to immunoglobulins or comparable substances, and acquired medical conditions known to cause secondary immune deficiency, such as chronic lymphocytic leukaemia, lymphoma, multiple myeloma, as well as protein losing enteropathies and hypoalbuminaemia. Patients with an active infection and receiving antibiotic therapy for the treatment of this infection at the time of screening or therapy with systemic steroids or other immunosuppressant drugs at the time of enrolment (current daily use of corticosteroids, i.e., >10 mg prednisone equivalent/day for >30 days) were also to be excluded. Intermittent corticosteroid use during the trial was allowable if medically necessary.

After an initial, up to 28-day screening period, patients were switched from their pre-trial IVIg replacement therapy to BT595 at the baseline visit. Patients were assigned to receive BT595 at doses between 0.2 and 0.8 g per kg body weight (bw) (2–8 ml/kg bw), either at a Q3W or Q4W schedule, for a treatment period of approximately 12 months. The dose and dosage interval had to be consistent with the patient's pre-trial IVIg treatment and was only to be changed if medically indicated. Efficacy and safety were assessed from baseline (Week 0) to the closing (follow-up) visit at Week 54 (Q3W schedule) or Week 56 (Q4W schedule).

For the first infusion, BT595 was administered as an intravenous infusion at an initial infusion rate of 0.3 ml/kg/h for 30 min, to be increased to 1.4 ml/kg/h for a further 30 min. If well tolerated, the infusion rate could then be gradually increased to a maximum of 2 ml/kg/h for the remainder of the infusion. From the second infusion onwards, patients' infusion rates could be gradually increased to a maximum of 8 ml/kg/h at the investigator's discretion, following the initial infusion rate of 0.3 ml/kg.

Patients who are prone to AEs occurring in conjunction with the infusion of IVIg products are often premedicated with antihistamines, antipyretics, and/or steroids. In this trial, the use of premedications to prevent AEs was to be avoided if possible, except in cases where such premedication was important for the safety of the patient.

Pharmacokinetics

Blood samples were collected with procedures adapted for each age category. A home care service was allowed for the PK sampling of paediatric patients.

Serum samples for detailed steady-state PK analysis were taken pre-dose before infusion 7 or infusion 5 of the Q3W or Q4W schedule, respectively, and at a series of fixed time points after this infusion according to their age category; therefore the number of blood draws depended on the patient's age category. Time points for patients 6 to <76 years were: pre-dose (10–30 min before infusion), 10–30 min post-infusion, 4 and 24 h post-infusion; and 4, 7, 14 and 21 days (for the Q3W and Q4W schedule), and 28 days post-infusion (Q4W schedule only).

For young children (2 to <6 years), optional sparse PK sampling at selectable time points within the specified time windows following the infusion was carried out. Evaluable data from ≥20 adult patients and all available paediatric data were included in the dense PK analysis. Analyses of IgG trough levels, concentration versus time profiles, and non-compartmental PK analyses (NCAs) were performed to assess the PK profile for total IgG, IgG subclasses 1–4, and 6 analysed antigen-specific IgGs (i.e., anti-pneumococcal capsular polysaccharide, anti-haemophilus influenzae type B, anti-measles, anti-tetanus, anti-cytomegalovirus and anti-hepatitis B surface antigen [anti-HBs]/hepatitis B). The blood samples taken for PK analysis were analysed by a central laboratory using standard methodology.

Statistical analysis

The statistical analysis was performed using SAS® Software version 9.4. The safety set (SAF) included all patients who received at least one dose of trial medication and was used for safety evaluation. The full analysis set (FAS) was used for efficacy evaluation and was identical to the SAF.

Seventy patients were planned to be enrolled in the trial to ensure a minimum sample size of 50 evaluable patients, including at least 20 paediatric and at least 20 adult patients, following the EMA guidelines [11]. This ensured a power of at least 80% to reject the null hypothesis of ≥1 SBI/subject/year. A one-sided one-sample Poisson test with a type I error of 0.01 was chosen, assuming a true underlying SBI rate of 0.5 per subject/year.

The proportion of infusions associated with ≥1 infusional AE was calculated, and the exact upper one-sided 95% confidence interval (CI) limit was compared to the threshold of 0.40 specified in the FDA Guidelines [8].

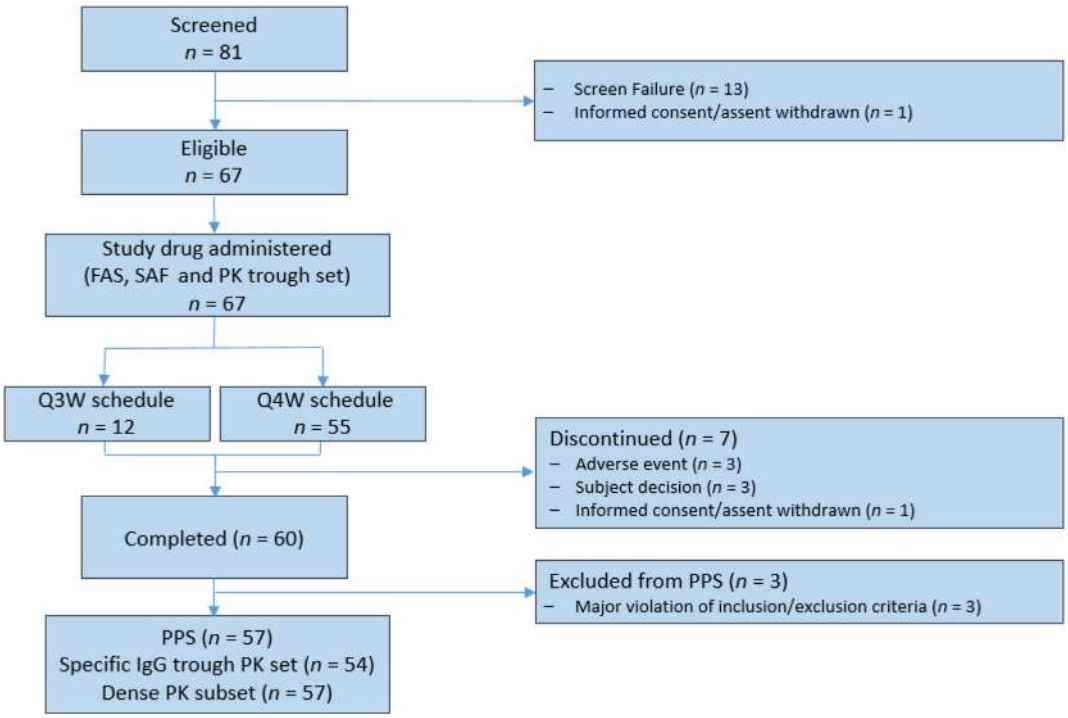

FIGURE 1 Patient disposition. FAS, full analysis set; *n*, number of patients in a specified category; PK, pharmacokinetics; PPS, per protocol set; Q3W, every 3 weeks; Q4W, every 4 weeks; SAF, safety analysis set

Data and safety monitoring board

To monitor the safety data from adult patients and provide advice and recommendations on the enrolment of paediatric patients, a DSMB consisting of independent experts was convened. The paediatric cohort was opened for enrolment after acceptable safety and tolerability had been demonstrated in ≥10 adult patients (18 to <76 years) who had received ≥2 BT595 infusions with no safety concerns.

RESULTS

Patient demographics

A total of 81 patients were screened and enrolled (Figure 1). Of these, 67 patients were eligible, treated and included in the FAS and SAF. Patients were enrolled from 4 October 2016, and the last patient was enrolled on 1 April 2020. Patients were treated in 17 sites on three continents (Table 1); 49 patients (73.1%) were adults, including 5 geriatric patients (≥65 years), and 18 patients (26.9%) were paediatric patients (2 to 16 years). Further details of patient characteristics are given in Table 2.

Among the patients, 53 were diagnosed with CVID and 13 with XLA. One additional patient had a specific other antibody defect and was allowed to participate in the trial. The types of diagnoses differed between age groups. Adults and adolescents predominantly had a diagnosis of CVID (46 adults, including all 5 geriatric patients; 5 adolescents). The paediatric patients aged <12 years predominantly were diagnosed with XLA (9 of 12 patients). Demographic characteristics were similar between the various age groups, the Q3W and Q4W schedule groups, males and females, and the patients from different regions.

The most frequently documented concomitant medical history (preferred terms) that occurred in ≥5% of the patients, excluding immunodeficiencies, were: drug hypersensitivity (17 patients [25.4%]); gastroesophageal reflux disease, hypertension (each 13 patients [19.4%]); arthralgia (10 patients [14.9%]); rhinitis allergic (9 patients [13.4%]); asthma, hypothyroidism (each 8 patients [11.9%]); chronic sinusitis, depression, migraine (each 7 patients

TABLE 1 Number of patients enrolled by continent and country

Continent/country (*n*)	Q3W *N* = 12	Q4W *N* = 55	FAS *N* = 67
United States	7	14	21
Europe	5	36	41
Hungary	1	27	28
Germany	1	3	4
Spain	3	0	3
Russian Federation (Europe)	0	6	6
Asia (Russian Federation)	0	5	5

Abbreviations: FAS, full analysis set; *N*, number of patients; *n*, number of patients in a specified category; Q3W, 3-week schedule; Q4W, 4-week schedule.

TABLE 2 Demographics and disease characteristics at baseline

Characteristics	Patients in FAS ($N = 67$)
Gender (*n*, %)	
Male	37 (55.2)
Female	30 (44.8)
Age at screening (years)	
Mean (SD)	34.6 (19.97)
Median	37.0
Minimum, maximum	2–74
Age group (*n*, %)	
2–16 years	18 (26.9)[a]
Adults	49 (73.1)
65 years and older	5 (7.5)
Race (*n*, %)	
Caucasian	66 (98.5)
Asian	1 (1.5)
Type of diagnosis (*n*, %)	
CVID	53 (79.1)
XLA[b]	10 (14.9)
Congenital agammaglobulinaemia[b]	2 (3.0)
Congenital hypogammaglobulinaemia[b]	1 (1.5)
Other[c]	1 (1.5)
Time since diagnosis [months]	
Mean (SD)	92.1 (98.93)
Total IgG trough level at baseline (g/L)	
Mean (SD)	8.23 (2.87)
Median	7.90

Abbreviations: FAS, full analysis set; *N*, number of patients; *n*, number of patients in a specified category; SD, standard deviation.
[a]Due to this age distribution, the number of patients qualifying as adolescents and adults complied with both, FDA and EMA age group categorizations (defined as 12 to <17 years according to FDA [15], and 12 to <18 years according to EMA guidance [16]).
[b]XLA, congenital agammaglobulinaemia, and congenital hypogammaglobulinaemia are all synonyms for hereditary hypogammaglobulinaemia. Therefore these patients met the inclusion criterion of having XLA.
[c]One additional patient had a specific other antibody defect, and was allowed to participate in the trial.

[10.4%]); osteoarthritis, insomnia (each 6 patients [9.0%]); bronchitis chronic, vitamin D deficiency, anaemia, iron deficiency anaemia (each 5 patients [7.5%]); bronchiectasis, irritable bowel syndrome, rhinitis, hypercholesterolaemia, hyperlipidaemia, anxiety, headache, postmenopause, fatigue (each 4 patients [6.0%]).

A total of 60 patients (89.6%) completed the trial. Seven patients discontinued early, three due to the decision of the patient, and informed consent was withdrawn for one paediatric patient. Three adult patients discontinued due to serious adverse events (SAEs) of a mild anaphylactic reaction, severe worsening of neutropenia, and mild toxic hepatitis, respectively.

BT595 treatment

Twelve patients received BT595 on a Q3W schedule and 55 patients on a Q4W schedule. Overall, 26,746 g of trial medication were administered, with a mean (SD) dose of 28.2 (10.23) g per infusion. The mean (SD) actual dose administered per infusion calculated across all patients and all infusions was 0.46 (0.13) g/kg bw. Patients received a mean (SD) number of 13.8 (3.47) infusions leading to a total of 923 infusions over a mean (SD) period of exposure of 341.7 (85.37) days (median 365 days), resulting in a total exposure of 67.59 subject-years.

In this trial, premedication before the first infusion was only used in single patient who had previous history of infusional reactions.

Primary end point

A single adult patient (Q4W) experienced one event classified as an SBI; this was described as aspiration pneumonia occurring following aspiration in the context of reflux after a single event of alcohol ingestion the night prior to the onset of symptoms. The event was classified as an SBI as the FDA criteria [8] were met: the patient had two clinical symptoms of bacterial pneumonia, namely cough and fever, and pneumonia was confirmed by X-ray.

The primary efficacy end point was met: The unadjusted SBI rate was 0.01 per subject-year, and therefore well below the predefined threshold of <1.0 SBI per patient per year set by EMA and FDA. The adjusted SBI rate (accounting for the length of the observation period) was 0.015 per subject-year, with an upper limit of the one-sided 99% CI of 0.151.

Secondary end points

The mean and median total IgG trough levels remained almost constant throughout the trial in both schedule groups. The average IgG trough levels stayed well above the targeted minimal trough level of 5 g/L. In the Q3W schedule group, the mean (SD) trough level was 10.1 (2.68) g/L at baseline and remained unchanged up to the follow-up visit after the last BT595 infusion with 10.4 (2.62) g/L. In the Q4W schedule group, the mean (SD) trough level was 7.8 (2.77) g/L at baseline. Trough levels increased to 8.3 (2.59) g/L before the second infusion and then remained stable up to the follow-up visit with 8.5 (2.22) g/L.

In the FAS, 48 patients (71.6%) experienced 189 infections overall; 19 patients (28.4%) remained infection-free. Most of the infections were assessed to be mild or moderate in severity. Four of these infections reported in 3 patients were SAEs requiring hospitalization. They included two adults, one with anal abscess and one with chronic sinusitis, and a 3-year-old child with appendicitis and gastrointestinal viral infection. Treatment-emergent infections (PTs by decreasing frequency) that were reported at least once by ≥10% of all patient were nasopharyngitis (16 patients [23.9%], 24 events), upper respiratory

TABLE 3 Secondary infection-related end points (FAS, $N = 67$)

Parameter	Number of events	Number of patients (%)	Annual rate per subject-year	Annualized rate per patient; mean (SD)
Any treatment emergent infection	189	48 (71.6)	2.80	2.63 (3.05)
Stratified by season				
Spring ($N = 66$)	52	33 (50.0)	3.02	3.00 (4.25)
Summer ($N = 63$)	32	23 (36.5)	1.96	2.22 (3.70)
Autumn ($N = 63$)	37	26 (41.3)	2.20	2.24 (3.34)
Winter ($N = 65$)	68	31 (47.7)	3.95	3.62 (6.00)
Non-serious infection	185	47 (70.1)	2.74	
Antibiotic treatment (including prophylactic)	115	39 (58.2)	32.58[a]	36.12 (88.5)[b]
Number of days on antibiotic treatment per patient				
None		28 (41.8)		
≥1 to <7		6 (9.0)		
≥7 to <14		11 (16.4)		
≥14 to <21		3 (4.5)		
≥21 to <35		6 (9.0)		
≥35 to <70		8 (11.9)		
≥70 to <365		3 (4.5)		
≥365		2 (3.0)		
Time lost from school/work[c]	292	26 (38.8)	4.32[a,d]/2.60[a,e]	3.99 (11.00)[b]
Any hospitalization	8	6 (9.0)	0.70[a]	0.80 (3.248)[b]
Hospitalizations due to infections	4	3 (4.5)	0.36[a]	0.06 (0.276)[b]
Fever episodes		14 (20.9)	1.69[a]	1.56 (3.91)[b]

Abbreviation: SD, standard deviation.
[a]Days per patient-year.
[b]Annualized number of days.
[c]Due to infections and their treatment.
[d]One year = 365 days.
[e]One year = 220 school/working days.

tract infections (13 patients [19.4%], 24 events), bronchitis (8 patients [11.9%], 12 events), sinusitis (8 patients [11.9%], 11 events), pharyngitis (7 patients [10.4%], 8 events) and viral upper respiratory tract infection (7 patients [10.4%], 7 events). Further infection-related parameters results are summarized in Table 3.

The median time to resolution of infections as per Kaplan–Meier analysis was 7.0 days (95% CI: 7.0–8.0 days). The median time to resolution tended to be longer in the adult and adolescent patients than in the two subgroups of younger children and also tended to be longer in the Q3W schedule group than in the Q4W schedule group. The majority of treatment-emergent adverse events (TEAEs) resolved within <14 days, and 44 infections (23.3%) lasted ≥14 days.

In the FAS, 28 patients (41.8%) required no antibiotic treatment for infections during the trial. The remaining patients received a total of 115 antibiotic treatment episodes, including both prophylactic and therapeutic administrations. Six patients either received prophylactic treatment throughout the trial (two patients; 399 and 409 days) or for a certain time period (one patient; started before the first infusion, imputed 43 days, imputation due to missing stop date), or who received regular antibiotics for pre-existing conditions (two patients with chronic bronchitis and one patient with Lyme disease; 314, 57 and 189 days, respectively).

A total of 41 patients (61.2%) did not lose any time from school/work due to infections and their treatment. Of the 26 patients (38.8%) with any time lost from school/work, 15 patients (22.4%) lost <7 days, 6 patients (9.0%) lost 7 to <14 days, 2 patients (3.0%) lost 14 to <21 days, and 3 patients lost ≥21 days (85, 40, and 21 days, respectively). The mean (SD) annualized rate of days lost was 3.99 (11.00) days per patient.

The majority of all patients (61 patients, 91.0%) did not require any hospitalization during the trial, and there were no hospitalizations for ≥21 days. Regarding hospitalizations due to any infection, 3 of 67 patients (4.5%) required a total of 4 hospitalizations with overall 24 hospitalization days.

Throughout the trial, 53 patients (79.1%) remained fever-free. The remaining 14 patients (20.9%) had 27 fever episodes, with a total of 114 fever days. This resulted in a mean (SD) annualized rate of 1.56 (3.912) fever days per patient and an overall annual rate of 1.69 fever days per subject-year.

Assessment of HR-QoL indicated a stable high level. The majority of adult and paediatric patients reported no problems in the five dimensions (mobility, self-care, usual activities, pain or discomfort, anxiety/depression) of the 3-levels EuroQoL Health questionnaire (EQ-5D-3L™) and the youth version (EQ-5D-Y™) at baseline (range between 50% up to 87.5% and 66.7% up to 100%, respectively) and up to the time of the last protocol-defined infusion (range between 65.9% up to 85.4% and 91.7 up to 100%, respectively), and no clinically relevant changes were observed from baseline to the last protocol-defined infusion. Mean EQ-VAS ratings indicated a stable high level or minor improvements.

Safety

Overall, 63 patients (94.0% [90% CI: 86.9–97.9%]) experienced 458 TEAEs; the majority were mild or moderate in severity and not related to trial medication. These included four events of an extra dose administered in four patients who received an additional final infusion in violation of the protocol. Four patients experienced a total of four severe TEAEs, of which three were not related to trial medication (i.e., acute appendicitis, thermal burn, radius fracture). A 22-year-old female in the Q3W schedule group developed an infusional TEAE/SAE of severe worsening of neutropenia after the first infusion. The relevant medical history for this patient consisted of thrombocytopenic purpura (approx. 14 years before the trial), thrombocytopenia and neutropenia (both ongoing for several months). In the last year before the event, there was a tendency of decreased neutrophil values based on haematology counts taken prior to IVIg infusions. The patient remained clinically asymptomatic, did not receive any treatment, and was discontinued from the trial. The neutropenia count returned to baseline level on Day 8. For the next treatment, the patient received conventional IVIg. Following this infusion, a similar course was observed: The neutrophil count dropped post-infusion, and the patient stayed clinically asymptomatic.

TABLE 4 TEAEs during infusion by infusion rate (SAF, $N = 67$))

Maximal administered infusion rate in ml/kg/h	Patients, *n* (%)	Number of patients with TEAEs during infusion, *n* (%)
≤0.3	1 (1.5)	10 (14.9)[a]
>0.3 to ≤1.4	2 (3.0)	2 (3.0)
>1.4 to ≤2	8 (11.9)	4 (6.0)
>2 to ≤4	21 (31.3)	3 (4.5)
>4 to ≤6	8 (11.9)	0
>6	27 (40.3)	0

[a]TEAEs at infusion rate ≤0.3 ml/kg/h include eight TEAEs for which a causal relationship to BT595 is unlikely or not plausible (extra dose administered (4), injection site extravasation (1) and imputations (nasal ulcer (1), urinary tract infection (1), oral pain (1))).

The maximum infusion rate of 8 ml/kg/h was used at the discretion of the investigator in 27 of the 67 patients (40.3%), and 25 of these reached this rate at ≥5 infusions. The number of TEAEs during infusion at related maximum infusion rates is given in Table 4. None of the infusional AEs with an onset during the infusion occurred during infusions with infusion rates of >4.0 ml/kg/h.

The duration of infusions decreased with increasing infusion rates, from a median of 174 min (infusion 1) to 122 min (last protocol-defined infusion) in the Q3W schedule group and from a median of 165 min to 94 min in the Q4W schedule group. The majority of the 923 infusions were completed without interruption or infusion rate reduction. Overall, four patients (6%) modified or interrupted four infusions (0.43%) due to TEAEs.

There were no fatal AEs. No patients required rescue medication for the underlying PID during the trial. Nine patients (13.4%) had a total of 12 treatment-emergent SAEs, of which two were assessed as related to trial medication; these events comprised a mild anaphylactic reaction during the first infusion (treated with prednisolone 60 mg and drotaverine 2 mg; heart rate and blood pressure normalized about 45 min after the start of the event) and the event of worsening of neutropenia mentioned above. Both patients discontinued the trial. Overall, 24 patients (35.8%) reported a total of 44 TEAEs that were assessed as related to trial medication (adverse drug reactions [ADRs]) (Table 5). All ADRs were infusional AEs of mild or moderate severity except for the severe events mentioned above.

Across all patients, 74 of all 923 infusions (8.0% [upper limit of the one-sided 95% CI: 9.6%]) were associated with ≥1 infusional AE,

TABLE 5 Related treatment-emergent adverse events (ADRs) that occurred more than once (SAF, $N = 67$)

	Q3W ($N = 12$)		Q4W ($N = 55$)		Overall ($N = 67$)	
Preferred term	*n* (%)	*E*	*n* (%)	*E*	*n* (%)	*E*
Any ADR	6 (50.0)	18	18 (32.7)	26	24 (35.8)	44
Headache	2 (16.7)	7	7 (12.7)	8	9 (13.4)	15
Fatigue	3 (25.0)	6	0	0	3 (4.5)	6
Chills	1 (8.3)	1	1 (1.8)	1	2 (3.0)	2
Extra dose administered	0	0	4 (7.3)	4	4 (6.0)	4
Blood pressure increased	0	0	3 (5.5)	3	3 (4.5)	3

Abbreviations: ADR, adverse drug reaction; *E*, number of events; *N*, number of patients; *n*, number of patients with event; Q3W, 3-week schedule; Q4W, 4-week schedule.

mainly headache (2.4%), fatigue (0.9%) and nausea (0.5%). This was well below the FDA-required safety threshold of 40% [8] and compared favourably with the frequency of 15.5%, 14.2% and 28.0% reported in similar PID studies [12–14]. The proportion of BT595 infusions associated with ADRs was 3.9%, mostly headache (1.6%) and fatigue (0.7%). The proportion of patients reporting infusional AEs was highest during or after the first infusion (19.4%) and then decreased over time (infusion 5: 4.7%).

There was no cluster of unexpected AEs, no thromboembolic event and no haemolysis was reported by the investigators.

Pharmacokinetics

Patients' mean total IgG levels at steady-state remained well above the targeted minimal trough level of 5 g/L throughout the dosing interval, with higher mean trough levels in the Q3W schedule group (10.0 g/L) than in the Q4W schedule group (8.27 g/L) as expected. No notable differences in trough levels were identified compared with patients' previous IVIg treatment. Exploratory equivalence testing (ANOVA) indicated that the steady-state total IgG trough levels for BT595 and previous IVIg were equivalent. The steady-state trough levels for IgG subclasses 1–4 and the six analysed antigen-specific IgGs followed the same pattern as observed for total IgG.

The steady-state total IgG PK profile after BT595 administration as determined by NCA based on the data from 57 patients aged 6 to <76 years resulted in a long half-life of >20 days (mean $t_{1/2}$ of 24.2 and 31.1 days in the Q3W and Q4W schedule group, respectively) and a low clearance (mean clearance of 0.09 and 0.08 L/day). Further PK parameters are given in Table S1 [17–22]. The Q3W and Q4W scheduling achieved sufficient concentrations of IgG, IgG subclasses 1–4, and the six analysed antigen-specific IgGs, exceeding the minimum recommended IgG level needed to effectively prevent infections. For two of the six antigen-specific IgGs tested (anti-tetanus and anti-cytomegalovirus), trough values were significantly higher versus the previous IVIg reference therapy ($p < 0.001$), both for the overall population and for the subgroup of adults. Additional NCAs based on various reduced datasets revealed no relevant findings, illustrating the robustness of the PK data derived from the full dataset.

DISCUSSION

Overall, the efficacy results of this trial demonstrate that BT595, a new, highly purified 10% preparation of normal human immunoglobulin for intravenous administration (IVIg), is effective, safe and well-tolerated as replacement therapy in PID patients with antibody deficiency. A single adult patient experienced one event (i.e., aspiration pneumonia) classified as an SBI. The primary efficacy end point was met with an overall annual SBI rate of 0.01 per patient-year. This was in line with SBI rates published in five recent similar PID-studies, where the SBI rates ranged between 0 and 0.080 SBIs per patient-year (Table S2), although the validity of direct comparison may be limited by differences in trial designs.

The outcomes of the secondary efficacy end points were consistent with the product being effective and supported the efficacy of BT595 in all age groups.

The proportion of patients with any time lost from school/work (38.8%) was consistent with the proportions observed in other studies (Table S2). The annual rate of days lost from school/work (4.32 days per patient-year) was at the upper end of the range in the five other studies (1.66–3.99 days per subject-year) because of five patients with ≥14 days lost from school/work, including a single patient who lost 85 days. This patient had 4 different fever episodes and 18 different infections of various types, including 2 SAEs that required hospitalization for 19 days (appendicitis) and 1 day (gastrointestinal viral infection), respectively.

The overall proportion of patients requiring antibiotic treatment throughout the trial (58.2%) was relatively low compared to the other five studies, where the proportion varied between 61.3% and 90.2% of patients. IgG trough levels remained almost constant throughout the trial in both schedule groups and stayed well above the targeted minimal trough level of 5 g/L. Changing IVIg treatment to BT595 was associated with a stable high level or minor improvements in HR-QoL.

BT595 was well tolerated in all age groups assessed, with no clinically relevant differences in safety parameters between adults, paediatric, or geriatric patients. There were no safety concerns. The patterns observed in relation to the severity and frequency of TEAEs did not differ from those reported with other IVIg preparations, and the ADRs observed were consistent with the known safety profile of IVIg preparations. The escalation of infusion rates up to 8 ml/kg/h was well tolerated, illustrating that this individualized approach was associated with a good adaptation to high infusion rates. Only one patient required a single premedication, and there were no infusional AEs at infusion rates of >4.0 ml/kg/h.

BT595 demonstrated PK properties in line with the well-characterized PK profile of other licensed IVIg products using similar doses (Table S1).

In summary, the results of this pivotal Phase-III trial demonstrate that BT595 is effective and safe as a replacement therapy for PID patients in preventing infections. Patients of all age groups achieved similar efficacy outcomes. BT595 is therefore an effective, convenient, safe and well-tolerated treatment option for patients of all age groups with PID who require replacement IVIg treatment.

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CONFLICT OF INTEREST

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ORCID

Christiane Staiger https://orcid.org/0000-0001-8687-7687

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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ORIGINAL ARTICLE

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Clinical and in vitro evaluation of red blood cells collected and stored in a non-DEHP plasticized bag system

Christie Vermeulen[1] | Gijs den Besten[2] | Annegeet G. van den Bos[3] | Mya Go[1,4,5] | Eric Gouwerok[1,4,5] | Richard Vlaar[1,4,5] | Martin R. Schipperus[6] | Saskia E. Spelmink[6] | Mart Janssen[7] | Johan W. Lagerberg[1,4,5] | Dirk de Korte[1,4,5] | Thomas R. L. Klei[1]

[1]Department of Product and Process Development, Sanquin Blood Bank, Amsterdam, The Netherlands

[2]Department of Clinical Chemistry, Isala Hospital, Zwolle, The Netherlands

[3]Department of Laboratory Medicine, Radboud University Medical Centre, Nijmegen, The Netherlands

[4]Department of Blood Cell Research, Sanquin Research, Amsterdam, The Netherlands

[5]Landsteiner Laboratory, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

[6]Department of Transfusion Medicine, Sanquin Blood Bank, Amsterdam, The Netherlands

[7]Transfusion Technology Assessment Unit, Donor Medicine Research Department, Sanquin Research, Amsterdam, The Netherlands

Correspondence
Christie Vermeulen, Department of Product and Process Development, Sanquin Blood Bank, Plesmanlaan 125, 1066CX Amsterdam, The Netherlands.
Email: c.vermeulen@sanquin.nl

Abstract

Background and Objectives: Di-ethyl-hexyl-phthalate (DEHP) is currently the main plasticizer used for whole blood collection systems. However, in Europe, after May 2025, DEHP may no longer be used above 0.1% (w/w) in medical devices. DEHP stabilizes red cell membranes, thereby suppressing haemolysis during storage. Here we compared in vitro quality parameters of red cell concentrates (RCCs) collected and stored in DEHP-, DINCH- or DINCH/BTHC-PVC hybrid blood bags with saline-adenine-glucose-mannitol (SAGM) or phosphate-adenine-glucose-guanosine-saline-mannitol (PAGGSM) storage solution. Last, we performed haemovigilance surveillance for RCC collected in DINCH-PVC and stored in PAGGSM/BTHC-PVC.

Materials and Methods: In vitro quality parameters of RCC were determined during 42 days of storage. Haemovigilance surveillance was conducted to compare the frequency and type of transfusion reaction.

Results: Haemolysis levels were increased in SAGM/BTHC-PVC as compared to SAGM/DEHP-PVC (0.66% ± 0.18% vs. 0.36% ± 0.17%). PAGGSM storage solution was able to adequately suppress haemolysis to levels observed during storage in SAGM/DEHP-PVC, both in BTHC-PVC (0.38% ± 0.12%), and to a slightly lesser extent in DINCH-PVC (0.48% ± 0.17%). A total of 1650 PAGGSM/BTHC-PVC and 5662 SAGM/DEHP-PVC RCC were transfused yielding a transfusion reaction frequency of 0.24% (95% CI 0.0000–0.0048) and 0.44% (95% CI 0.0027–0.0061) respectively.

Conclusion: The in vitro quality of RCC stored in PAGGSM/BTHC-PVC and SAGM/DEHP-PVC is comparable. There is no indication that transfusion of erythrocytes stored in PAGGSM/BTHC-PVC results in increased transfusion reaction frequency. These initial results provide a basis for further clinical evaluation to narrow down the confidence interval of transfusion reaction frequency.

Keywords

haemovigilance surveillance, in vitro blood quality parameters, non-DEHP, red cell concentrates, transfusion reactions

Highlights

- The absence of DEHP leads to increased haemolysis in SAGM.
- Storage of erythrocytes in PAGGSM/BTHC-PVC results in similar haemolysis levels compared to storage in SAGM/DEHP-PVC.
- Transfusion of RCCs stored in PAGGSM/BTHC-PVC does not result in an increased rate of transfusion reactions.

INTRODUCTION

Since the 1950s, di-ethyl-hexyl-phthalate (DEHP) has been the plasticizer used to confer favourable physical characteristics to blood bag systems made of polyvinyl chloride (PVC). In the last decade, several studies have shown that DEHP may be toxic, at least in rodents, negatively impacting fertility rates at certain dosages [1]. As such, the European Medical Device Regulation, a regulation that governs medical device safety and quality, has banned DEHP application in medical devices above 0.1% (w/w) with expected sunsetting in May 2025. Currently, many blood establishments and research groups, along with the manufacturers, are exploring various plasticizer and storage solution alternatives, with the goal of transitioning to non-DEHP blood collection and storage bags without affecting blood component quality [2–5]. Simultaneously the toxicity of the DEHP-alternative, the leaching rate and the impact on physical characteristics of the blood bag set are important parameters to be considered.

The lowest reported no-adverse-effect level (NOAEL) for DEHP is 4.8 mg/kg body weight per day, leading to reproductive impairment of female rats when continuously exposed during the critical stages of gestation. However, acute toxicity of DEHP is very low, with an LD50 of more than 25 g/kg in rats and mice [6]. The daily exposure of the general population to DEHP through the environment and food is steadily declining every year as it is being banned from more and more applications. The Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) report estimated that, based on the specific study and age group, DEHP exposure might range from 2 to 50 μg/kg body weight per day, which is well below the lowest reported NOAEL in animal studies [6]. Acute exposure to DEHP, for example, during exchange transfusions may peak temporarily above the lowest reported NOAEL but still remain far below levels associated with acute toxicity [6]. As such, these considerations should also be taken into account when searching for suitable DEHP alternatives.

Several DEHP alternatives have been explored over the last decade, with N-butyryl-n-hexyl citrate (BTHC), 1,2-cyclohexane dicarboxylic acid diisononyl ester (DINCH), di(2-ethylhexyl) terephthalate (DEHT) and trioctyltrimellitate (TOTM) being the most prominent [3–5, 7, 8]. Much is already known about their impact on the physical characteristics of blood bag systems and tubing, as well as their toxicity compared to DEHP, as is reviewed in the SCENIHR report [6]. For example, BTHC requires a 52 times higher daily dose for haematological changes and impact on liver weight to occur [6]. For both DINCH and TOTM, a 20 times higher daily dose is required in order for kidney/thyroid impairment and adenoma formation in the uterus [6]. In addition, leaching of DINCH and TOTM into the blood components is reported to be severalfold lower, further reducing the risk of toxic effects occurring [6].

With regard to product quality, it is recognized that DEHP has little to no effect on platelet and plasma component quality [3, 4]. Conversely, it is clear that DEHP has the off-target effect of stabilizing red cell membranes, thereby suppressing haemolysis during storage [9, 10], as well as affecting morphology, osmotic resistance and recovery [9–11]. As such, the quality of standard red cell concentrates (RCCs), as well as their derivatives, such as irradiated RCC, are the focus of attention in the pursuit of a DEHP alternative. It was shown before that the use of next-generation storage solutions, such as the additive solution phosphate-adenine-glucose-guanosine-saline-mannitol (PAGGSM) and the Additive Solution Formula 3 (AS-3), could improve the stability of red cells during storage in non-DEHP storage bags [2, 3].

In this study, we verified in vitro quality parameters of RCC collected in DEHP-, DINCH- and DINCH/BTHC-PVC hybrid blood bags and subsequently stored in DEHP-, DINCH- and BTHC-PVC storage bags with saline-adenine-glucose-mannitol (SAGM) or PAGGSM as an additive solution. Following this, we started the implementation of standard production procedures of the DINCH/BTHC-PVC hybrid blood bag system and PAGGSM/BTHC-PVC RCC storage bags (Table 1) to collect data from routine use. Finally, we initiated

TABLE 1 Description of the whole blood collection bag and RBC storage conditions used for the in vitro studies and haemovigilance surveillance

	Whole blood collection bag	Storage solution and RBC storage bag plasticizer
Condition 1[a]	DEHP-PVC (CQC2988)	SAGM/DEHP-PVC
Condition 2[a]	DINCH-PVC (hybrid GQ422NL)	PAGGSM/BTHC-PVC
Condition 3[b]	DINCH-PVC (GQ42271)	SAGM/BTHC-PVC
Condition 4[b]	DINCH-PVC (GQ42271)	PAGGSM/ DINCH-PVC

Abbreviations: BTHC, N-butyryl-n-hexyl citrate; DEHP, di-ethyl-hexyl-phthalate; DINCH, 1,2-cyclohexane dicarboxylic acid diisononyl ester; PAGGSM, phosphate-adenine-glucose-guanosine-saline-mannitol; PVC, polyvinyl chloride; RBC, red blood cell concentrate; SAGM, saline-adenine-glucose-mannitol storage solution; WB, whole blood.
[a]Conditions used for in vitro studies and haemovigilance surveillance.
[b]Conditions used for in vitro studies only.

haemovigilance surveillance of which the primary objective was to assess the safety in terms of transfusion reactions of RCC collected in the DINCH/BTHC-PVC hybrid blood bag system and stored in PAGGSM/BTHC-PVC storage bags. We compared transfusion reaction frequency to the RCC collected and stored in SAGM/DEHP-PVC. Moreover, transfusion reactions were classified in terms of category, seriousness, imputability and clinical outcome. Secondary objectives were the evaluation of user issues, such as leakage and spiking, both in the clinic and during the production of the blood components.

METHODS

In vitro analysis

Whole blood

All blood donors met standard donation criteria and gave their written informed consent in accordance with the institution's guidelines and practices. The studies were approved by the institutional medical ethical committee in accordance with the Declaration of Helsinki.

Whole blood (WB), 500 ml ± 2%, was collected in steam-sterilized DINCH-PVC or DINCH/BTHC-PVC hybrid quadruple bags, bottom-and-top collection systems containing 70 ml Citrate-phosphate-dextrose (GQ42271, GQ422NL, Fresenius Kabi, Germany). The RCC storage bag of these systems was made from either DINCH-PVC or BTHC-PVC, while all other bags were DINCH-PVC. Collection and storage conditions for the in vitro studies are detailed in Table 1. WB units were placed on butane-1,4-diol cooling plates (CompoCool, Fresenius Kabi, Germany) to allow their temperature to adjust from 20 to 24°C. After the overnight hold, WB was processed according to the routine buffy coat procedure as previously described [12]. Briefly, after a hard spin, the WB was separated into components using an automated blood component separator (CompoMat G5, Fresenius Kabi, Germany). RCC was diluted with 110 ml SAGM or PAGGSM and white blood cells were reduced using the inline leukoreduction filter (Bioflex RCC DEHT, Fresenius Kabi, Germany). For the paired comparison of in vitro quality during storage in DINCH-PVC and BTHC-PVC, two units of ABO-compatible RCC were pooled and equally divided over the two bags.

As a reference, WB was collected and processed into the same components as mentioned above with the routinely used systems, that is, DEHP-PVC collection systems (CQC2988, Fresenius Kabi, Germany), with SAGM as RCC additive solution.

Red cell concentrates

Leukoreduced RCC was sampled and analysed on the day of production and on Day 42 of storage at 2–6°C. Haematological parameters were analysed on Advia 2120 haematology analyser (Siemens Medical Solutions Diagnostics, Breda, the Netherlands). Free haemoglobin (Hb) was determined by absorbance measurement of cell supernatants at 415 nm, with correction for plasma absorption if more than 2% plasma was present. Cell supernatants were obtained by double centrifugation of the RCC suspensions (5 min at 12,000×g and resulting supernatant again 5 min at 12,000×g for 5 min). Haemolysis was expressed as a percentage of total Hb present in RCC after correction for haematocrit.

Extracellular potassium, glucose, lactate and pH were measured using a blood gas analyser (Rapidlab 1265, Siemens Medical Solutions Diagnostics). Adenosine triphosphate (ATP) levels were determined in neutralized perchloric acid extracts using the glucose/hexokinase reaction as described elsewhere [13].

Plasticizer analysis

For extracting the plasticizer, an RBC sample was mixed with acetonitrile and hexane. After phase separation, the upper hexane phase containing the plasticizers was analysed. Plasticizer analyses were performed by an external laboratory (Fresenius HemoCare Netherlands, Emmer-Compascuum) with gas chromatography using DEHP, BTHC and DINCH as internal standards.

Haemovigilance surveillance

Design and ethical approval

A prospective observational cohort study, starting in October 2021, was performed in Isala Hospital Zwolle and Radboud University Medical Center, Nijmegen, a general hospital and an academic hospital, respectively. The criterion for inclusion was 18 years or older patients receiving non-irradiated RCC. Collection and storage conditions for the RCC used are detailed in Table 1. Participating hospitals received a mix of RCC collected in DEHP-PVC blood bag systems and stored in SAGM/DEHP-PVC, and RCC collected in DINCH/BTHC-PVC hybrid blood bag systems and stored in PAGGSM/BTHC-PVC. Products were randomly issued to patients. Patients received exclusively one product type (i.e., standard or non-DEHP). Deviations from this protocol have been reported in Tables 4 and 5 under 'combination group'. The Committee on Research Involving Human Subjects (CMO) region Arnhem-Nijmegen (Radboud University Medical Center) evaluated the protocol according to the Medical Research Involving Human Subjects Act (WMO) and General Data Protection Regulation (in Dutch: Algemene Verordening Gegevensbescherming).

Data collection and outcomes

Dutch hospitals reported transfusion reactions to the National Hemovigilance and Biovigilance office for TRIP (Transfusion and Transplantation Reactions in Patients). Transfusion reactions were defined and reported according to the current guidelines for blood transfusion and definitions as used by TRIP (https://www.tripnet.nl/en/hemovigilance/definitions-2/).

Participating hospitals allowed data-sharing (pseudo-anonymous) of reported transfusion reactions with Sanquin Blood Bank (SBB) by

selecting the option in Tripnet. TRIP periodically generated an overview of reference numbers of reported transfusion reactions by the participating hospitals. SBB generated an export from Tripnet and annotated the reported transfusion reactions to the product used.

The primary outcome was the number of reported transfusion reactions for RCC in PAGGSM/BTHC-PVC and RCC in SAGM/DEHP-PVC. Transfusion reactions were classified by category, seriousness (grade 0–4), imputability (certainly not—probably not—possibly—probably—certainly) and clinical outcome (complete recovery—mild remnant symptoms—severe remnant symptoms—death). Furthermore, user issues in the clinic as well as during the production of blood components were captured in a routine data capture system (TrackWise Digital Quality Management Software).

Data were handled and stored according to the General Data Protection Regulation. Only dedicated users from SBB had access to the data. Data will be stored within the SBB ICT environment for 30 years.

Sample size

For the sample size calculation, the average transfusion reaction frequency for both participating hospitals over a period of 5 years was used as a reference (0.29%). Incidents (errors/failures during transfusion) and antibody formation were excluded. In this study, we opted for a manageable sample size of 8000 transfusions, which would allow us to detect a significant increase in transfusion reaction rate exceeding 0.8%. Detecting smaller differences would therefore require a larger sample size. The sample size calculation was based on an alpha of 0.05 and a beta of 0.8. Based on these numbers and assumptions, 1541 transfusions per arm (PAGGSM/BTHC-PVC vs. SAGM/DEHP-PVC) were required at a minimum. A total of 1650 RCC units stored in PAGGSM/BTHC-PVC and 5662 RCC units stored in SAGM/DEHP-PVC were ultimately issued.

TABLE 2 Alert and termination levels for various monitoring points

	Alert level					Termination level				
Monitoring point	Transfusion reactions	Proportion	Bayes factor	False positives (%)	False negatives (%)	Transfusion reactions	Proportion	Bayes factor	False positives (%)	False negatives (%)
300	4	1.3	12.7	1.2	45	5	1.7	75	0.2	65
1000	9	0.9	7.8	0.2	8	10	1	40	0.1	15
1500	12	0.8	3	0.1	2	14	0.9	73	0.0	6
Sum				1.5					0.3	

TABLE 3 RBC quality parameters at Days 1 and 42 of storage in SAGM and PAGGSM

Whole blood collection bag RBC storage bag Storage solution	DEHP-PVC DEHP-PVC SAGM ($n = 30$)	DINCH-PVC BTHC-PVC SAGM ($n = 20$)	DINCH-PVC BTHC-PVC PAGGSM ($n = 88$)	DINCH-PVC DINCH-PVC PAGGSM ($n = 37$)
Day 1				
Hb (g/L)	193 ± 10 (194)	198 ± 6.5 (194)	194 ± 5.9 (194)	192 ± 7.5 (194)
Hct (L/L)	0.61 ± 0.03 (0.61)	0.64 ± 0.01[a] (0.64)	0.63 ± 0.02[a] (0.63)	0.61 ± 0.01[b] (0.61)
MCV (fL)	95 ± 6.0 (97)	101 ± 3.3[a] (100)	99 ± 4.0 (99)	96 ± 3.3[b] (96)
ATP (μmol/g Hb)	5.7 ± 0.6 (5.1)	5.5 ± 0.8 (5.4)	5.1 ± 0.5 (5.1)	5.3 ± 0.5 (5.2)
Day 42				
Hct (L/L)	0.65 ± 0.02 (0.65)	0.65 ± 0.01 (0.65)	0.64 ± 0.02 (0.64)	0.62 ± 0.02 (0.62)
MCV (fL)	103 ± 5.4 (104)	106 ± 3.5[a] (106)	101 ± 4.2[a] (102)	98 ± 2.6[a,b] (98)
Haemolysis (%)	0.36 ± 0.17 (0.33)	0.66 ± 0.18 (0.65)	0.38 ± 0.12 (0.37)	0.48 ± 0.17[b] (0.47)
ATP (μmol/g Hb)	3.3 ± 0.5 (3.4)	3.5 ± 0.5 (3.5)	3.9 ± 0.5[a] (4.0)	4.0 ± 0.5[a] (4.0)
DEHP (mg/L)	27.6 ± 7.9 (25.3)	<0.1	<0.1	<0.1
BTHC (mg/L)	Not determined	11.0 ± 2.6 (10.2)	9.6 ± 1.8 (9.3)	Not determined
DINCH (mg/L)	Not determined	Not determined	2.9 ± 1.2 (2.4)	7.5 ± 2.9 (9.0)

Note: Data shown as mean ± SD (median).

Abbreviations: ATP, adenosine triphosphate; BTHC, N-butyryl-n-hexyl citrate; DEHP, di-ethyl-hexyl-phthalate; DINCH, 1,2-cyclohexane dicarboxylic acid diisononyl ester; hb, haemoglobin; Hct, hematocrit; MCV, mean corpuscular volume; PAGGSM, phosphate-adenine-glucose-guanosine-saline-mannitol; PVC, polyvinyl chloride; SAGM, saline-adenine-glucose-mannitol storage solution; RBC, red blood cell concentrate.

[a] $p < 0.05$ as compared to SAGM/DEHP-PVC (Student's unpaired *t*-test).

[b] $p < 0.05$ as compared to PAGGSM/BTHC (Student's unpaired *t*-test).

Study conduct and blinding

Interim analyses were planned at monitoring points during the study to ensure a timely response to an unexpected high transfusion reaction rate. We took into consideration the standard low rate of transfusion reactions, and as a consequence, the high range of uncertainty of reported transfusion reaction percentages after low numbers of transfusions in our study. By taking into consideration these uncertainties, a Bayesian non-inferiority design for a transfusion reaction rate of 0.29% was applied for monitoring where termination of the study would ensue upon adverse event rates exceeding 1.7% after 300 transfusions, 1% after 1000 transfusions and 0.9% after 1500 transfusions, with alert levels at 1.3%, 0.9% and 0.8% respectively (Table 2) [14]. Although it was unlikely that patients and physicians would recognize differences in the products issued, we could not fully exclude this possibility as International Society of Blood Transfusion (ISBT) numbers on products often differ.

Statistics

Categorical data are expressed as the number of observations and percentage. Statistical analyses were performed with standard software (Microsoft Excel, Bellevue, MA, USA). Results are shown as mean ± SD with the number of observations given between parentheses; *t*-tests were used to determine the significance of differences between two groups. A *p*-value of less than 0.05 was considered significant.

RESULTS

RCC quality during storage

First, we aimed to assess the impact of the substitution of DEHP-PVC by BTHC-PVC in combination with the SAGM storage solution (conditions 1 and 3, as detailed in Table 1). A significant increase in haemolysis was found on Day 42 (0.36% ± 0.17% vs. 0.66% ± 0.18%), while ATP levels remained similar. Leaching of DINCH and BTHC into the RBC, as measured at Day 42 of storage, was significantly lower as compared to DEHP (Table 3). The changes in pH, extracellular potassium, glucose and lactate concentrations during storage were comparable for both storage bags (not shown).

In order to suppress haemolysis during storage in BTHC-PVC, we substituted the SAGM storage solution with PAGGSM (conditions 2 and 3, as detailed in Table 1). This managed to dampen haemolysis on Day 42 from 0.66% ± 0.18% to 0.38% ± 0.12%, which is comparable to haemolysis levels observed in SAGM/DEHP-PVC (0.36% ± 0.17%). Additionally, ATP levels were significantly better maintained during storage in PAGGSM as compared to SAGM. We subsequently compared the storage of RCC in BTHC-PVC with DINCH-PVC in combination with the PAGGSM storage solution (conditions 2 and 4, as detailed in Table 1) (Table 3). With a mean value of 0.48% ± 0.17% at Day 42, storage in DINCH-PVC resulted in slightly but significantly higher levels of haemolysis as compared to storage in BTHC-PVC (0.38% ± 0.12%). ATP levels at Day 42 were comparable in both groups.

TABLE 4 Demographic characteristics of the transfusion reaction patients and blood group of RCC issued

Variable			Value
Gender			
Males			19 (63%)
Females			11 (37%)
Age (years)			
Range			44–88
Mean age ± SD			71 ± 9
Range males			60–88
Mean age males ± SD			71 ± 7
Range females			44–88
Mean age females ± SD			72 ± 12
Blood group of transfusion reaction patients split by product type issued	**RCC in PAGGSM/BTHC-PVC**	**RCC in SAGM/DEHP-PVC**	**Combination of both product types**
A−		1	
A+	1	13	1
B+		2	
O+	2	9	1
Blood group of RCC issued	**RCC in PAGGSM/BTHC-PVC**	**RCC in SAGM/DEHP-PVC**	
A−	67	381	
A+	515	2041	
B−	36	85	
B+	37	356	
O−	279	744	
O+	706	1990	
AB−	3	27	
AB+	7	38	
Total	1650	5662	

Abbreviations: BTHC, N-butyryl-n-hexyl citrate; DEHP, di-ethyl-hexyl-phthalate; PAGGSM, phosphate-adenine-glucose-guanosine-saline-mannitol; PVC, polyvinyl chloride; RCC, red cell concentrates; SAGM, saline-adenine-glucose-mannitol storage solution.

Haemovigilance surveillance

Based on the positive outcome of the in vitro data obtained from RCC collected in the DINCH/BTHC-PVC hybrid blood bag system and stored in PAGGSM/BTHC-PVC, we selected this non-DEHP alternative to conduct haemovigilance surveillance. During the study period, a total of 7312 RCC units were issued to 2285 patients (1650 RCC units in PAGGSM/BTHC-PVC and 5662 RCC units in SAGM/DEHP-PVC)

TABLE 5 The number of RCC issued and the frequency of transfusion reactions in the RCC in PAGGSM/BTHC-PVC, the RCC in SAGM/DEHP-PVC and the combination group

Product	Number of products issued	Number of patients received RCC transfusion	Number of transfusion reactions	Transfusion reaction rate per 100 transfusions (95% CI)
Total number of RCC	7312	2285	30	0.41 [0.0026–0.0056]
RCC in PAGGSM/BTHC-PVC	1650	652	4	0.24 [0.0000–0.0048]
RCC in SAGM/DEHP-PVC	5662	1633	25	0.44 [0.0027–0.0061]
Combination group[a]			1	
Isala Hospital				
Total number of RCC	3971	1264	20	0.50 [0.0028–0.0072]
RCC in PAGGSM/BTHC-PVC	798	327	2	0.25 [−0.0010 to 0.0060]
RCC in SAGM/DEHP-PVC	3173	937	17	0.54 [0.0029–0.0079]
Combination group[a]			1	
Radboud University Medical Center				
Total number of RCC	3341	1021	10	0.30 [0.2845–0.3155]
RCC in PAGGSM/BTHC-PVC	852	325	2	0.23 [0.2017–0.2583]
RCC in SAGM/DEHP-PVC	2489	696	8	0.32 [0.0010–0.0054]

Abbreviations: BTHC, N-butyryl-n-hexyl citrate; CI, Confidence interval; DEHP, di-ethyl-hexyl-phthalate; PAGGSM, phosphate-adenine-glucose-guanosine-saline-mannitol; PVC, polyvinyl chloride; RCC, red cell concentrates; SAGM, saline-adenine-glucose-mannitol storage solution.
[a]Two patients developed a transfusion reaction after receiving both types of RCC within 24 h. For one patient the reaction developed after administration of the first product (RCC in PAGGSM/BTHC), therefore included in the RCC/BTHC-PVC group. The second one was a delayed haemolytic transfusion reaction which could not be linked to one product type, therefore included in the combination group.

TABLE 6 List of category of transfusion reactions, grouped by seriousness (grade 0–4), according to the RCC product issued

		Number of reactions	
Product	Category	Grade 1	Grade 2
RCC in PAGGSM/BTHC-PVC	Non-haemolytic transfusion reaction	3	-
	Other	-	1
RCC in SAGM/DEHP-PVC	Non-haemolytic transfusion reaction	13	1
	Other	5	3
	Post transfusion bacteraemia/sepsis	2	-
	Transfusion associated dyspnea	1	-
Combination group[a]	Delayed haemolytic transfusion reaction	-	1

Abbreviations: BTHC, N-butyryl-n-hexyl citrate; DEHP, di-ethyl-hexyl-phthalate; PAGGSM, phosphate-adenine-glucose-guanosine-saline-mannitol; PVC, polyvinyl chloride; RCC, red cell concentrates; SAGM, saline-adenine-glucose-mannitol storage solution.
[a]Patient received both types of RCC.

(conditions 1 and 2, as detailed in Table 1). Both products were issued to the hospitals within 9 days, and standard transfusion protocols were followed.

All RCCs fulfilled the routine standard quality control requirements of SBB. During the processing of the blood components, no breaking and leakage of non-DEHP blood collection and storage bags were reported. No user issues were reported by participating hospitals.

In Table 4, the demographic characteristics of the patients that developed a transfusion reaction are summarized. The age of the patients ranged from 44 to 88 years, with a mean age of 71. Male preponderance (63%) was noted. The frequency of transfusion reactions in patients that had received RCC stored in either PAGGSM/BTHC-PVC or SAGM/DEHP-PVC is listed in Table 5. Of all 2285 patients, 30 developed a transfusion reaction. The rate of transfusion reactions was lower in the PAGGSM/BTHC-PVC group as compared to the SAGM/DEHP-PVC group. Two patients developed a transfusion reaction after receiving both products. Of these two, the first transfusion reaction is included in the PAGGSM/BTHC-PVC group because the patient's fever had already developed after the administration of this product. The second transfusion reaction was a delayed haemolytic transfusion reaction. Because this reaction could not be linked to one product type, it is included in the combination group (Table 5). We

TABLE 7 Imputability of the transfusion reactions, grouped by category and seriousness (grade 0–4), according to the RCC product issued

			Imputability[b]			
Product	**Category**	**Seriousness**	**Certainly not**	**Probably not**	**Possibly**	**Probably**
RCC in PAGGSM/BTHC-PVC	Non-haemolytic transfusion reaction	Grade 1		1	2	
	Other	Grade 2		1		
RCC in SAGM/DEHP-PVC	Non-haemolytic transfusion reaction	Grade 1		1	8	4
		Grade 2		1		
	Other	Grade 1			2	3
		Grade 2	1	1		1
	Post transfusion bacteraemia/sepsis	Grade 1		1	1	
	Transfusion associated dyspnoea	Grade 1			1	
Combination group[a]	Haemolytic transfusion reaction	Grade 2				1

Abbreviations: BTHC, N-butyryl-n-hexyl citrate; DEHP, di-ethyl-hexyl-phthalate; PAGGSM, phosphate-adenine-glucose-guanosine-saline-mannitol; PVC, polyvinyl chloride; RCC, red cell concentrates; SAGM, saline-adenine-glucose-mannitol storage solution.
[a]Patient received both types of RCC.
[b]None of the transfusion reactions had an imputability of certainly.

also categorized the different types and grades of transfusion reactions according to TRIP classification (Table 6). Non-haemolytic transfusion reactions were the most common (57%). One patient had transfusion-associated dyspnoea, and two patients had post-transfusion bacteraemia/sepsis after administration of an RCC unit in SAGM/DEHP-PVC. Most transfusion reactions were grade 1; only six were grade 2. Table 7 shows the imputability of the transfusion reactions grouped by category and seriousness per administered product. Only mild to moderate reactions (grade 1 or 2) were reported in both groups. All four reactions reported in PAGGSM/BTHC-PVC group had a low imputability (probably not or possibly). Two patients had a grade 2 transfusion reaction probably related to the transfusion product. In the first case, it concerns a rise in blood pressure (category 'other') after administration of an RCC unit in SAGM/DEHP-PVC; in the second case, it concerns a delayed haemolytic transfusion reaction after administration of both products. Of all the patients that developed a transfusion reaction, 100% completely recovered.

DISCUSSION

With the DEHP ban due to become effective from May 2025, exploration of possible alternative plasticizers is becoming a pressing issue. From previous work, it can be concluded that there is no evidence suggesting that the quality of plasma and platelet components is negatively affected by the absence of DEHP [3, 4]. However, it is clear that the absence of the red cell-stabilizing effect of DEHP is a hurdle to overcome. Thus, instead of sacrificing blood product quality for a non-DEHP storage bag, the goal of this undertaking is to attain both; that is, a similarly high-quality, low haemolysis, red cell product, while simultaneously transitioning away from the use of DEHP in blood collection and storage bags. In attempts to attain this goal, the use of next-generation storage solutions is explored to compensate for the increased haemolysis levels observed in the absence of DEHP.

The combination of BTHC-PVC and PAGGSM is a promising candidate, allowing 42 days of storage with low rates of haemolysis. The low haemolysis rates at the end of storage were obtained without mixing by regular sampling or processing.

In this study, we have shown that the in vitro quality of red cells collected in the non-DEHP full DINCH-PVC or DINCH/BTHC-PVC hybrid blood bag system and stored in PAGGSM/BTHC-PVC during storage is similar, and to some extent, superior to that of red cells stored in SAGM/DEHP-PVC. Haemolysis levels were shown to be similar during storage, whereas ATP content, a predictive marker for circulation duration after transfusion, was superior in PAGGSM/BTHC-PVC stored red cells. These data were used as a basis to start small-scale standard implementation of RCC production in PAGGSM/BTHC-PVC. Through the haemovigilance surveillance, we established that the incidence of transfusion reactions for red cells stored in PAGGSM/BTHC-PVC did not exceed that of those stored in SAGM/DEHP-PVC. The most common transfusion reaction observed in our study was a non-haemolytic transfusion reaction. Reported reactions were mild to moderate, with low imputability. The observations for red cells stored in PAGGSM/BTHC-PVC were consistent with historical data.

These data, taken together, provide a basis for further exploration of the non-DEHP DINCH/BTHC hybrid blood bag system. A higher number of transfusions are to be performed to further narrow down the confidence interval of non-DEHP storage of RCC on transfusion reaction frequency. It is also important to gather data on the effect of secondary processing steps, such as, for example, RCC irradiation, on in vitro quality parameters in the absence of DEHP. Aside from secondary processing steps, niche issues, such as, for example, the effect of lipemic plasma on red cell quality during storage, may require re-evaluation, in order to answer the question to what degree DEHP-free RCCs are resilient in those types of conditions.

In parallel to the non-DEHP transition, anticoagulant and storage solution-containing blood bag systems are up-classified from class 2b to class 3, which was recently endorsed by the European Commission. This means that the approach to the clinical evaluation of blood products in

non-DEHP collection and storage bags is going to be changed. Currently, however, there exists no guidance on what this clinical evaluation should pertain to. To our knowledge, the only guidance document that touches upon this subject is 06-MDCG-2020 (on reg. 2017/745), but this guidance document focuses on clinical evidence needed for medical devices previously CE-marked under directive 93/41/EEC and 90/385/EEC. As such, it is currently unclear what type of clinical evidence (i.e., haemovigilance surveillance or recovery studies) will be required for newly CE-marked medical devices. What is clear, however, is that the transition will be an enormous undertaking, with a tremendous amount of possible plasticizer/storage solution combinations and a large number of (sub)components requiring investments both in time and cost to facilitate. Simultaneously we have to strive for the best possible outcome, that is, ensure the continued supply of high-quality blood components, also in the absence of DEHP. International collaboration on this front may prove to be vital in meeting the deadlines currently put forward by the European Commission.

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T.K., C.V., J.L., M.S. and S.S. designed the study and wrote the protocol; E.G., R.V. and M.G. contributed to performing the experiments and acquisition of the in vitro data; M.J. designed the haemovigilance strategy; G.d.B. and A.v.d.B. contributed in performing the haemovigilance surveillance; T.K., D.d.K., C.V., J.L., M.S. and S.S. analysed the data and wrote the paper. The authors agreed to the final submitted version.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

ORCID

Christie Vermeulen https://orcid.org/0000-0003-4575-2874
Mart Janssen https://orcid.org/0000-0002-1682-7817

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ORIGINAL ARTICLE

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In vitro storage characteristics of neonatal platelet concentrates after addition of 20% PAS-E

Christine V. Saunders | **Nicola B. Pearce** | **Chloe George**

Welsh Blood Service, Llantrisant, UK

Correspondence
Christine V. Saunders, Welsh Blood Service, Ely Valley Road, Talbot Green, Llantrisant CF72 9WB, UK.
Email: christine.saunders2@wales.nhs.uk

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Abstract

Background and Objectives: An observed decline in end-of-storage pH in plateletpheresis-derived platelet concentrates for neonatal use suspended in 100% autologous plasma was expected to be reversed by the addition of a platelet additive solution, (PAS)-E, increasing unit volume by approximately 20%. This study determined the impact on other in vitro storage parameters to ensure the expected increase in pH did not mask an adverse impact on component quality.

Study Design and Methods: For each replicate, one of a pair from a double adult dose plateletpheresis collection had approximately 50 ml of PAS-E added on Day 3 of storage. Its unmodified twin served as a control. Each adult dose was split into four neonatal storage packs and tested on Days 3, 6, 7 and 8. Three of 12 replicates were from donors with a history of low pH at end of storage and reflected the worst-case scenario for the new components. A further experiment evaluated whether any differences were simply due to the increased unit volume.

Results: In the nine randomly selected collections, pH on Day 8 was approximately 0.4 units higher in the test units. Platelet activation tended to be lower, with CD62P surface expression on Day 8 of 54.6 ± 9.9% compared to 65.8 ± 10.7% for controls ($p < 0.001$). Test units from donors with historically low pH retained $pH_{22°C}$ levels above 6.8 compared to controls (<6.4 on Day 8).

Conclusion: The addition of 20% PAS-E by volume increased the buffering capacity of the units whilst maintaining other in vitro storage characteristics.

Keywords

neonatal, pH, platelet additive solution, platelet concentrates

Highlights

- The Welsh Blood Service observed a decline in end-of-7-day-shelf-life pH in apheresis-derived platelet concentrates (PCs) for neonatal use.
- The addition of platelet additive solution (PAS)-E to apheresis PCs at a ratio of 80:20 plasma to PAS-E helped buffer pH levels whilst maintaining other in vitro quality indicators.
- Adoption of this component has allowed valuable donors to be retained on the neonatal PC panel.

INTRODUCTION

The Welsh Blood Service (WBS) obtained platelet concentrates (PCs) for neonatal use by aseptically splitting adult dose plateletpheresis collections suspended in 100% autologous plasma into paediatric storage packs. $pH_{22^{\circ}C}$ is used as an indicator of component quality, with UK Guidelines stipulating that more than 90% of units tested should have a pH of 6.4 or greater at end of storage [1]. Since the United Kingdom uses a system to monitor all PCs for bacterial contamination throughout the shelf life of the component, the shelf life for PCs at WBS is extended to midnight on Day 7 of storage. The WBS observed a decline in end-of-shelf-life pH in both primary adult dose and neonatal split apheresis-derived PCs, with a stepwise decrease in mid-2017 followed by a further decrease from mid-2018. A number of interventions were introduced, including (i) storing units label-side down on the agitators to improve gaseous exchange through the storage packs, (ii) increasing pick-ups of collections from the onsite Collection Clinic from two per day to three per day to reduce the time units were stored without agitation and (iii) omitting the use of plastic bags to transport the units from the Collection Clinic to the Manufacturing Laboratory. Collectively, these interventions led to a moderate increase in pH levels, but the percentage of neonatal units meeting the specification remained inconsistent. As part of the investigation into possible causes, it became evident that the collections from certain donors repeatedly showed lower levels of pH after a few days of storage [2]. However, even after excluding the results from these individuals from the data set, the end-of-storage pH levels were still failing to meet the required standard.

Discussions with other UK transfusion services confirmed that a similar issue was being experienced by other services. Colleagues from NHS Blood and Transplant (NHSBT; Cambridge, UK) proposed adding platelet additive solution (PAS) to the adult dose prior to splitting to produce a suspension medium with approximately 20% PAS-E and 80% autologous plasma. This is a conservative approach using an established commercial additive solution that could be implemented within the current manufacturing setup at WBS. The final component was expected to meet the specification for platelet yield and unit volume, allowing an effective clinical dose of platelets to be administered without increasing the transfused volume in neonates who have a small total volume. PAS-E solutions contain phosphate, which would be expected to act as a buffer and stabilize the pH [3]. To ensure that this practice would not mask any adverse impact on the quality of the components by simply maintaining buffered pH levels above 6.4, the WBS undertook a paired pool-and-split study comparing the in vitro storage characteristics of neonatal PCs stored in 100% autologous plasma against neonatal PCs stored in a medium with an 80:20 ratio of autologous plasma to commercial PAS-E (SSP+; Macopharma, Mouvaux, France). In addition, to determine whether any significant differences were simply due to the extra volume in the test units, a further experiment was performed in which a similar volume of autologous plasma was added to a 100% plasma unit.

METHODS

Selection and preparation of units

Double adult dose PCs were collected on the Trima plateletpheresis system (v6.3 software; Terumo Europe, Leuven, Belgium) from volunteer donors on the plateletpheresis panel. The study was prepared and approved following WBS standard operating procedures for undertaking a quality improvement study, including ethical consideration for the use of donations in studies aiming to improve the quality of blood components. Immediately after collection (Day 0), the units were approximately split into two adult doses and allowed to rest at ambient temperature for 3 h before being stored as adult doses at 22 ± 2°C with constant horizontal agitation. On Day 1, the units were pooled to obtain a sample for residual white cell counting and then accurately re-split by weight into two adult doses. A 16-ml sample was aseptically removed on Day 2 and used to inoculate an aerobic and anaerobic culture bottle. These were incubated for 7 days in a bacterial monitoring system (BacTAlert 3D™; BioMérieux UK, Basingstoke, UK). On Day 3, the two doses were randomly assigned to either the control or test arm of the study. Fifty millilitres of additive solution was added to the test unit by sterile connecting a pack containing the SSP+ solution. The control and test units were each evenly divided into four paediatric storage packs (VQE605B: Macopharma) and all the splits were irradiated (GSR C1 irradiator; Gamma Service Medical GmbH, Leipzig, Germany). One of the four neonatal splits from both the control and test arms was tested at each time point. Units were tested on Day 3 (after splitting and irradiation) and on Days 6, 7 and 8. Samples were collected aseptically from the units by sterile connecting a 20-ml sample pouch (MacoPharma).

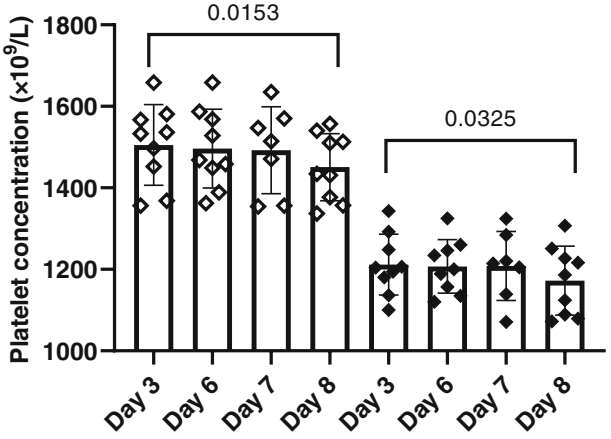

FIGURE 1 Platelet concentration in platelet concentrate from randomly selected plateletpheresis donors ($n = 9$ for all days except Day 7 when $n = 7$). Day 3 values statistically compared against Day 8 values using mixed effects model with $p < 0.01$ regarded as statistically significant. ◇, Control units in 100% plasma; ◆, test units in 20% PAS-E

Basic characteristics and sampling

Unit volume was calculated by subtracting the tare weight of the paediatric pack and dividing the net weight by the specific gravity of 1.03. Platelet concentration and mean platelet volume were measured on a haematology analyser (Pentra 80XL™; ABX Horiba, Montpellier, France), with platelet yield calculated as platelet concentration per unit volume. Leucoreduction was confirmed by flow cytometry (DNA-Prep kit; Beckman Coulter, CA, USA). Any units with pH levels below 6.4 were tested at end of storage to confirm sterility.

pH and metabolic parameters

pH, blood gases, glucose and lactate were measured on a biochemistry analyser (ABL 800 BASIC; Radiometer UK; Crawley, UK). pH levels are temperature-corrected to 22°C to reflect the storage temperature. All other parameters are reported at 37°C. Bicarbonate results were calculated from measured $pH_{37°C}$ and pCO_2 levels, based on the relationship between pH, [pCO_2] and [HCO_3^-] described by the Henderson–Hasselbalch equation [4].

Activation, function and morphology measures

Hypotonic shock response (HSR) and extent of shape change (ESC) were measured on a SPA-2000 aggregometer (Chronolog; PA, USA), with samples diluted with autologous plasma to a platelet concentration of 300×10^9/L. Swirling was assessed on a scale from 0 (no swirling) to 3 (strong swirling). Platelet activation was assessed by the surface expression of CD62P and aminophospholipids, measured by flow cytometry as previously described [5]. The latter are

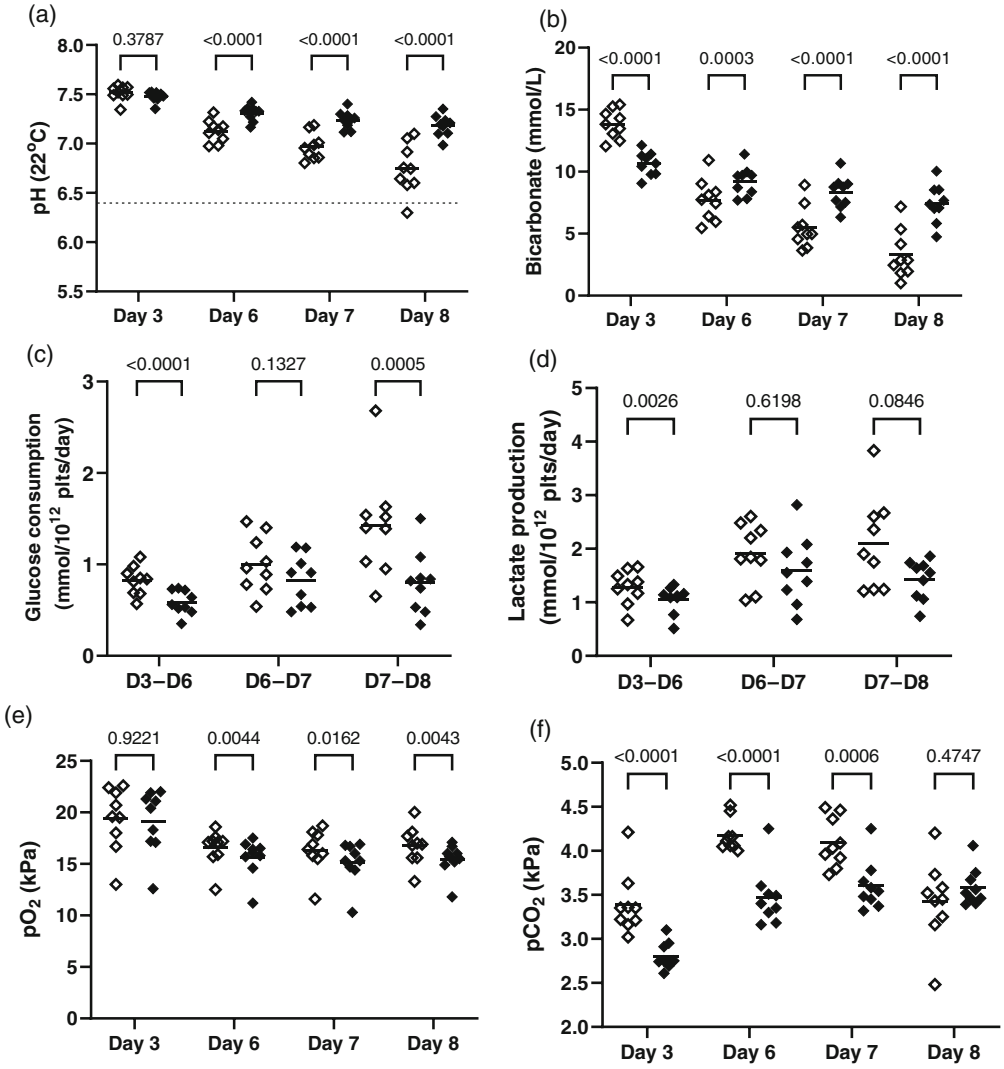

FIGURE 2 Metabolic indicators of platelet concentrate from randomly selected plateletpheresis donors ($n = 9$). (a) $pH_{22°}$, (b) bicarbonate, (c) glucose consumption, (d) lactate production, (e) pO_2 and (f) pCO_2. p values between the paired control (100% plasma) and test (20% PAS-E) units at each time point are reported. $p < 0.01$ are interpreted as statistically significant. ◇, Control units in 100% plasma; ◆, test units in 20% PAS-E

reported as the percentage of platelets binding annexin V; a protein that binds to aminophospholipids such as phosphatidylserine (PS) and phosphatidylethanolamine in a calcium-dependent manner [6].

Statistical analysis and experimental design

The study aimed to undertake 12 replicate experiments. However, the targeting of three donors with a history of low pH at end of storage means their results were not included in the general analysis or descriptive statistics. Results on storage characteristics from these donors are reported separately and individually. Results for the remaining nine units are quoted as mean ± standard deviation. Unless stated, statistical comparisons between pairs were undertaken with a two-way repeated measures analysis of variance (ANOVA), with a p value below 0.01 considered statistically significant (GraphPad prism v9.3; CA, USA).

RESULTS

Collection and processing of units ($n = 12$)

Twelve replicate experiments were completed, including three from donors whose collections had been previously found to have low pH levels at end of storage. The mean volume of SSP+ added to the test units was 47.5 ± 1.6 ml. The calculated percentage of SSP+ in the test units was 20.0 ± 0.9%, with a range of 17.8%–20.9%. Residual white cell counts in all units were below 1×10^6/unit and routine bacterial monitoring on all units was negative. The mean volume of the 48 split neonatal units in the control arm was 43.7 ± 2.3 ml compared to 55.6 ± 2.6 ml for the splits in the test arm. Within each arm of the study, no statistically significant differences were evident between the splits ($p = 0.759$ for controls and $p = 0.981$ for the test units; one-way repeated measures ANOVA).

Mean platelet yields in the Day 3 splits in the control and test units were $67.6 \pm 5.9 \times 10^9$/unit and $68.4 \pm 5.9 \times 10^9$/unit, respectively, with no statistically significant difference between the two study arms (paired t-test; $p = 0.586$). Mean platelet concentration of control units on Day 3 was $1531 \pm 99 \times 10^9$/L compared with $1230 \pm 76 \times 10^9$/L in test units. The percentage decrease in platelet concentration from Days 3 to 8 was proportionately similar in the two arms, being 3.5 ± 2.9% and 3.3 ± 3.1% of Day 3 values in control and test units, respectively (Figure 1).

In vitro storage characteristics of randomly selected plateletpheresis donors ($n = 9$)

Metabolic characteristics

After the addition of SSP+ on Day 3 to the test units, control units had marginally higher $pH_{22°C}$ levels than test units (7.51 ± 0.07 vs. 7.48 ± 0.05; $p = 0.379$). On Days 6, 7 and 8, levels were markedly

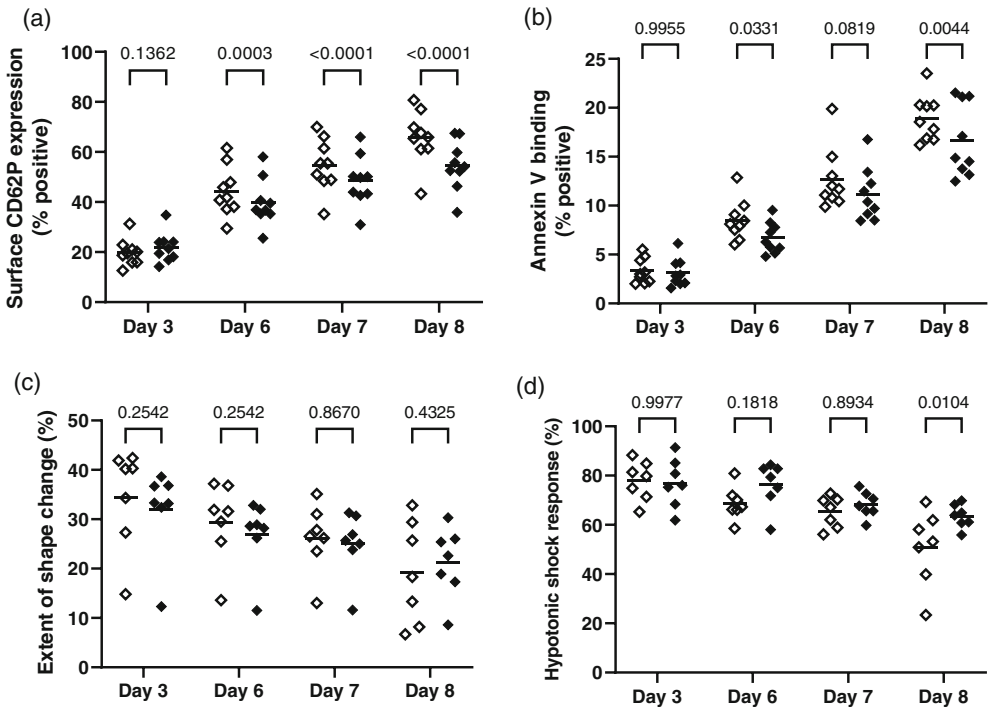

FIGURE 3 Platelet activation and indicators of platelet function in platelet concentrate from randomly selected plateletpheresis donors ($n = 9$ with exception of extent of shape change [ESC] and hypotonic shock response [HSR] and response to collagen, where $n = 7$). (a) Surface expression of CD62P, (b) annexin V binding to platelet, (c) ESC and (d) HSR. p values between the paired control and test units at each time point are reported. $p < 0.01$ are interpreted as statistically significant. ◇, Control units in 100% plasma; ◆, test units in 20% PAS-E

higher in the test units (Figure 2a), with mean $pH_{22°C}$ by Day 8 of 7.18 ± 0.11 in test units compared to 6.74 ± 0.25 in controls ($p < 0.001$). All nine test units had $pH_{22°C}$ levels above 6.4 on Day 8 and thus met the UK specification for a minimum of 90% of components to have pH ≥6.4 at end of storage. By contrast, one of the nine control units had $pH_{22°C}$ levels below 6.4 by Day 8. Mean levels of bicarbonate on Day 3 in the test units were approximately 23% lower than in the control units. This was primarily caused by the dilution of these units with SSP+, which does not contain bicarbonate. However, levels were better retained in the test units so that by Day 8 the mean level in test units was 7.4 ± 1.6 mmol/L compared with 3.3 ± 2.0 mmol/L in the control arm (Figure 2b).

Glucose levels on Day 3 were significantly lower in test units due to the dilution of the suspension medium (15.7 ± 1.4 mmol/L in control units vs. 12.5 ± 1.2 mmol/L; $p < 0.001$). By Day 8, however, no statistically significant difference was evident, with mean values of 8.3 ± 2.9 mmol/L and 8.4 ± 2.0 in control and test units, respectively ($p = 0.978$), suggesting the rate of glucose consumption was higher in the control units. This was confirmed by relating the change in glucose levels per day to the unit platelet concentration (Figure 2c). The consumption of glucose is inversely related to the production of lactate, with lactate levels increasing with storage. There was a tendency for the rate of lactate production to be lower in test units over the course of storage compared to control units. However, this did not translate to a statistically significant difference ($p = 0.085$); a reflection of the considerable variability between donors (Figure 2d).

pO_2 levels on Day 3 were similar in both arms (19.4 ± 3.1 kPa and 19.1 ± 3.1 kPa in control and test units, respectively [$p = 0.922$]). Levels had declined by Day 6 to approximately 16 kPa in both control and test units and remained relatively stable for the remainder of the storage period (Figure 2e). pCO_2 values in control units on Day 3 were 3.39 ± 0.35 kPa compared to 2.80 ± 0.15 kPa in test units ($p < 0.0001$).

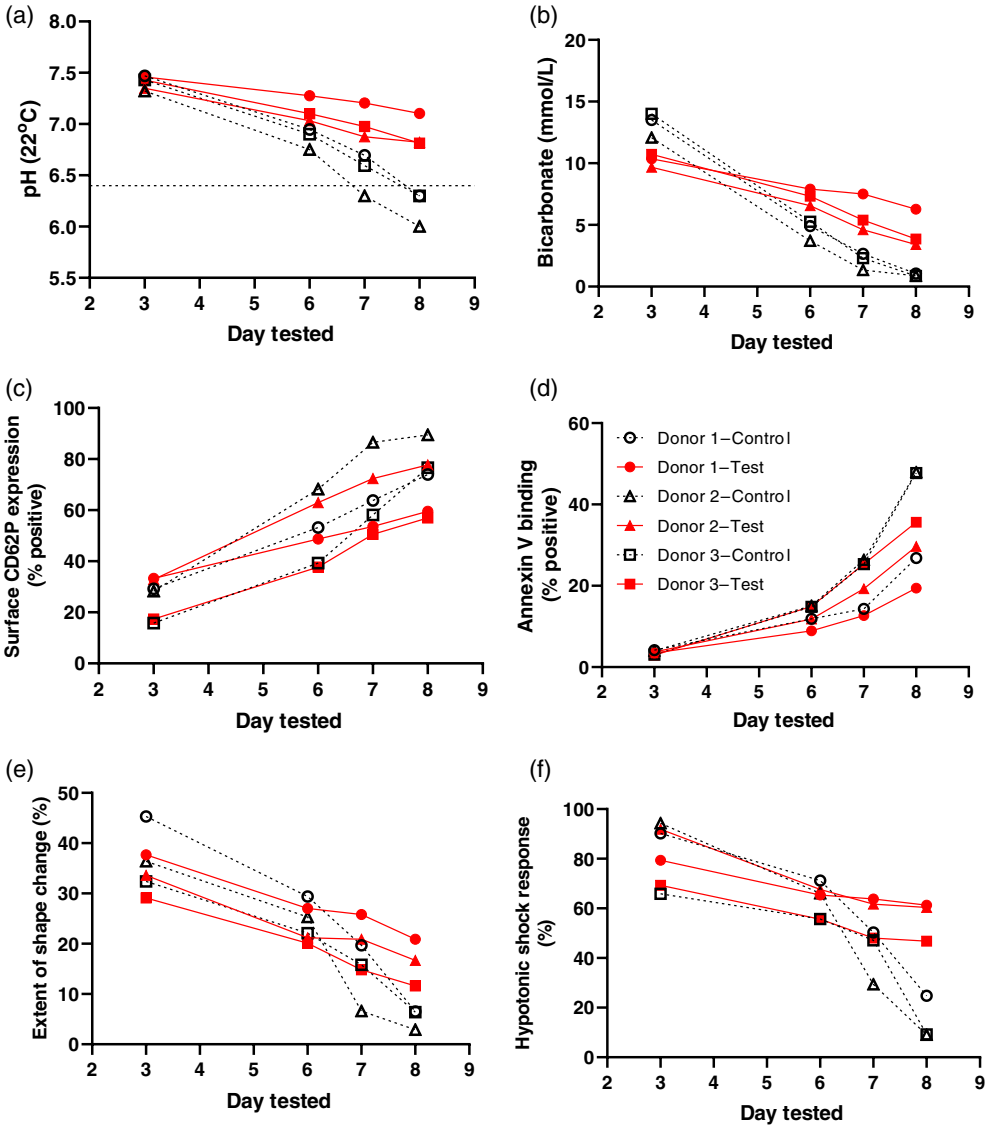

FIGURE 4 In vitro storage characteristics of platelet concentrate from three donors with a history of previous donations with low pH at end of storage. (The rate of change between Days 3 and 6 can only be inferred but is added for clarity.)

In controls, levels increased before declining between Days 7 and 8 whereas in test units, levels plateaued between Days 6 and 8 (Figure 2f).

Platelet function and morphology

Stronger swirling tended to be retained in the test units compared to control units. Poor swirling was noted throughout storage in one replicate, regardless of storage medium. Mean percentage expression of CD62P by the end of storage had increased to 65.8 ± 10.7% in the control arm compared to 54.6 ± 9.9% in test units ($p < 0.001$; Figure 3a). Binding of annexin V was similar in both arms of the study on Day 3 ($p = 0.996$). Subsequently, values tended to be higher in control units with a mean of 18.9 ± 2.3% on Day 8 versus 16.6 ± 3.7% in test units ($p = 0.004$) (Figure 3b). ESC and HSR declined with storage in both control and test units, but no statistically significant differences between the study arms were evident with either parameter (Figure 3c,d).

In vitro storage characteristics of units from donors with a history of low pH at end of storage ($n = 3$)

Results from the three collections from donors with a history of low pH at end of storage are presented individually in Figure 4a–f. By Day 6, $pH_{22°}$ levels were lower in all the control units compared to test units, and by Day 8, all control units had levels below 6.4 (with sterility confirmed). By contrast, $pH_{22°}$ levels in all three test units remained above 6.8 at end of storage (Figure 4a). Bicarbonate concentrations by Day 6 were also lower in the control units and continued to decrease at a faster rate, with concentrations below 1.5 mmol/L coinciding with pH levels below 6.4 (Figure 4b). By end of storage, platelet activation was higher in all three control units compared to their respective test units. The difference in surface CD62P positive expression from Day 3 to Day 8 was 16%–21% higher in the control units compared to the respective test units (Figure 4c). Similarly, the difference in annexin V binding was 7%–18% higher in the control units between Days 3 and 8 (Figure 4d). There was a steeper decrease in both ESC and HSR after Day 6 in control units, compared to test units (Figure 4e,f). Swirling by Day 8 was poor or absent in all three controls, whereas two of the three test units retained strong swirling throughout storage.

Role of increased volume

In this single experiment, approximately 37 ml of autologous plasma was added to the control and a similar volume of SSP+ was added to the test unit. The mean volume of the four test splits was 55.5 ± 0.7 ml compared to 54.3 ± 1.1 ml for the controls. $pH_{22°}$ levels decreased markedly with storage in the control unit, with levels on Day 8 below 6.4 in the control unit but retained above 6.9 in the test unit (Table 1). Rates of glucose consumption and lactate production were higher in the control unit. Strong swirling was retained in the test unit throughout storage, whereas only poor swirling was visible by Day 8 in the control. The control unit showed higher levels of activation after Day 3, with Day 8 CD62P expression of 84.4% compared to 65.1% in the test unit, and annexin V binding of 21.8% versus 17.9% in the test unit.

DISCUSSION

In response to the decline in pH levels at end of storage in apheresis-derived PCs for neonatal use, a PAS-E platelet additive solution

TABLE 1 Results of single experiment to determine the role of increased volume on the in vitro storage characteristics

	Day 3		Day 6		Day 7		Day 8	
	Control (100% plasma)	Test (20% PAS-E)	Control (100% plasma)	Test (20% PAS-E)	Control (100% plasma)	Test (20% PAS-E)	Control (100% plasma)	Test (20% PAS-E)
pH (22°C)	7.48	7.41	6.94	7.12	6.75	7.03	6.30	6.92
pO_2 (kPa)	18.4	17.0	15.0	13.6	14.9	16.5	15.9	14.9
pCO_2 (kPa)	3.27	3.05	5.21	4.42	4.55	4.07	3.98	4.06
Bicarbonate (mmol/L)	12.5	10.0	6.4	7.8	3.7	6.1	1.6	4.8
Glucose (mmol/L)	14.9	11.6	10.3	8.3	7.9	6.7	5.3	5.2
Lactate (mmol/L)	6.4	5.6	14.2	12.7	17	15	22	18
Swirling	3	3	3	3	2	3	1	3
Surface CD62P (% positive)	24.9	27.3	58.9	47.3	71.5	57.4	84.4	65.1
AV binding (% positive)	3.48	2.81	9.69	7.58	14.9	11.6	21.8	17.9
ESC (%)	37.4	37.8	26.6	28.2	20.4	22.2	9.3	18.0
HSR (%)	90.6	91.2	77.6	80.9	64.2	79.2	36.3	70.7

Abbreviations: ESC, extent of shape change; HSR, hypotonic shock response; PAS, platelet additive solution.

(SSP+) was added at a ratio of 20% PAS to 80% plasma to provide additional buffering capacity. This study was undertaken to determine the in vitro storage characteristics of platelets stored in this modified medium and ensure the expected retention of adequate end-of-storage pH did not mask an adverse impact on the quality of the component.

Guidelines for Transfusion Services in the United Kingdom state that PCs should have $pH_{22^\circ C}$ levels equal to or above 6.4 at end of storage [1]. This limit originated from publications that showed platelets were irreversibly damaged by pH levels below 6.2 [7, 8]. Changes included irreversible disc-to-sphere transformation, with most platelets reported as spherical with pH levels between 6.0 and 6.4 [9]. It is clear from the results that the addition of SSP+ to a ratio of approximately 80% plasma to 20% PAS-E stabilized pH levels in the test units. SSP+ contains phosphate and acetate at concentrations of 28.2 and 32.5 mmol/L, respectively. At concentrations of 10 mmol/L, phosphate has been found to act as a pH buffer in PCs [10, 11]. The acetate present as a source of oxidizable fuel also provides additional buffering capacity – its oxidation requires the conversion to an acidic form, removing an H^+ ion from the surrounding medium in the process. If the H^+ ion originated from carbonic acid, a bicarbonate ion would be generated, helping to retain levels of this physiological buffer in the medium [12, 13]. The ACD-A anticoagulant used to collect platelets by apheresis does not contain either phosphate or acetate, with the platelets relying principally on the bicarbonate in the plasma to buffer the concentration of H^+ ions. The higher levels of bicarbonate in the test units on Days 6–8 show that the added phosphate and acetate provided by the SSP+ solution were reducing the reliance on bicarbonate to maintain pH. By contrast, bicarbonate in the control units was essentially depleted by Day 8 in control units with pH levels below 6.4. This coincided with lactate concentrations of 23 mmol/L or above, corresponding with the established literature which states that there is sufficient bicarbonate in plasma to buffer the initial 20–25 mmol/L of lactate [14, 15]. The higher rate of loss of bicarbonate in control units is also reflected in the increased pCO_2 between Days 3 and 7 [16].

Platelet activation was measured by the surface expression of CD62P and by the binding of annexin V to aminophospholipids such as PS on the platelet surface. Both markers are increasingly expressed on the platelet surface following activation. CD62P plays a role in the recruitment of leucocytes to the site of injury and the delivery of platelet-derived pro-inflammatory mediators [17], whilst PS enhances the activity of pro-coagulant factors and has also been associated with the onset of apoptosis [18–21]. Although there was a tendency for platelet activation to be lower in test units compared to controls, of note is the large variation in activation between different donors, regardless of the storage medium. This variability may prove to have a bigger impact on the clinical effectiveness of individual components than the relatively modest change in suspension medium evaluated in this study.

ESC measures the change in light transmission through a platelet sample when ADP is added. This is generally interpreted as corresponding to the change in platelet shape associated with an increased exposure to ADP. HSR measures the change in light transmission when water is added to the sample which causes the platelet to swell. Viable platelets will slowly return to a more normal shape as they expel the water [22]. Both markers have shown a moderate correlation with in vivo platelet viability post-transfusion [23]. There was no statistically significant difference between the two arms of the study. Interestingly, one replicate showed poor responses with the ESC assay throughout storage in both the control and test units. These units also had poor swirling and MPV exceeding 10 fl throughout storage. Since these parameters are indicators of platelet shape it confirms that the platelets from this donation were morphologically different to those from the other donors in the study.

Three of the 12 collections were from donors whose units have previously resulted in low pH levels at end of storage on more than one occasion. These units were used to reflect the worst-case scenario expected for the new component. The results clearly showed pH levels were better maintained after the addition of SSP+, as were the levels of bicarbonate. Platelet activation by the end of storage was numerically lower in the test units compared to the corresponding control, whilst the indirect platelet function indicators of ESC and HSR were better maintained. It is not possible to state whether these differences would translate to a clinically more effective component, but the results suggest the quality of the components, as measured by these commonly adopted indicators, is at least comparable to the previously approved component suspended in 100% autologous plasma.

Donor-specific variation in the rates of glycolysis that ultimately affect pH values in stored PCs has been occasionally reported in the literature [24], though a lower platelet concentration has been posited as a possible counter to these observations [25]. An additional experiment was undertaken to determine whether the higher volume and lower platelet concentration in the test units were responsible for the differences between the two arms of the study. The targeting of a donor with a history of collections with low pH was used to exaggerate any differences and thus enable a qualitative evaluation of the question whilst minimizing the impact on stocks for clinical use. The results were consistent with the conclusion that it was the addition of SSP+, and not simply the increase in volume and associated lower platelet concentration, that maintained pH values.

The processing environment at WBS at the time of writing imposed some limitations on the manufacturing of this component. Ideally, components would be stored in a plasma:additive solution medium at the time of collection. Since this study, WBS has initiated a programme to evaluate the collection of apheresis-derived PC in a 65:35 ratio of PAS-E to plasma, as specified in the European Guidelines [26]. This would simplify the manufacturing of PC for neonatal and infant use whilst retaining the buffering capability of an appropriate PAS.

In summary, the addition of a PAS-E additive solution to apheresis PC at a ratio of 80:20 plasma to PAS-E increased the buffering capacity of the medium, allowing neonatal PC units to retain $pH_{22^\circ C}$ levels above 6.4 to end of storage whilst maintaining other in vitro storage characteristics. The WBS has introduced this component into routine use, allowing the Service to meet the required guidelines and retain valuable plateletpheresis donors on the neonatal panel.

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C.V.S. undertook testing, analysis and wrote the manuscript; N.B.P. undertook testing, data collation and reviewed the manuscript; C.G. critically reviewed the manuscript.

CONFLICT OF INTEREST

There are no conflicts of interest.

ORCID

Christine V. Saunders https://orcid.org/0000-0002-7010-6068

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ORIGINAL ARTICLE

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The abrogated role of premedication in the prevention of transfusion-associated adverse reactions in outpatients receiving leukocyte-reduced blood components

Yuan-Bin Yu[1,2,3] | Tai-Chen Lee[4] | Chun-Yee Ho[4] | Hui-Jung Lin[4] | Wei-Chi Chen[5,6] | Chih-Chun Chang[4,6,7]

[1]Division of Oncology and Hematology, Department of Internal Medicine, Far Eastern Memorial Hospital, New Taipei, Taiwan

[2]Faculty of Medicine, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan

[3]Graduate Institute of Medicine, Yuan Ze University, Taoyuan, Taiwan

[4]Department of Clinical Pathology, Far Eastern Memorial Hospital, New Taipei, Taiwan

[5]Public Health Bureau, New Taipei, Taiwan

[6]Department of Nursing, Cardinal Tien Junior College of Healthcare and Management, Yilan, Taiwan

[7]Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung University, Taoyuan, Taiwan

Correspondence
Chih-Chun Chang, Department of Clinical Pathology, Far Eastern Memorial Hospital, No. 21, Sec. 2, Nanya S. Road, Banqiao, New Taipei City, Taiwan.
Email: chihchun.chang1211@gmail.com

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Abstract

Background and Objectives: Although it remains controversial, premedication before transfusion is a common clinical practice to prevent transfusion-associated adverse reactions (TAARs) in Taiwan. Thus, we aimed to investigate whether premedication prevented outpatients from developing TAARs and whether an educational programme could improve the understanding of physicians related to the unnecessary use of premedication, and this could elicit changes in their prescribing activities without affecting the occurrence of TAARs.

Materials and Methods: Clinical data from outpatients receiving transfusion therapy, including predisposing diseases, histories of transfusion and TAARs, premedication and the occurrence of TAARs in the period April 2017 to October 2018, were retrospectively obtained. The evidence-based transfusion programme implemented to educate physicians was started in January 2018.

Results: A total of 5018 blood units were transfused to 803 outpatients, with 2493 transfusion events reported in the study interval. The most frequently transfused component was leukocyte-reduced packed red cells ($n = 4338$), followed by leukocyte-reduced apheresis platelets ($n = 540$) and other blood components. The overall premedication rate significantly decreased from 92.4% to 76.7% after the educational programme ($p < 0.001$). There was no remarkable change in the occurrence of TAARs per patient event between the periods before and after the educational programme (1.11% vs. 1.14%, $p = 0.964$). Besides, it was shown that the occurrence of TAARs was associated with the history of TAARs and inversely related to multiple transfusions, but not premedication.

Yuan-Bin Yu and Tai-Chen Lee contributed equally to this work.

Conclusion: Decreased premedication was not associated with increased incidence of TAARs in outpatients; these findings provide important evidence to support the need to revise clinical practices in the era of leukocyte-reduced blood products.

Keywords

antihistamines, antipyretics, leukocyte depletion, premedication, steroids, transfusion reactions

Highlights

1. Decreased premedication was not associated with increased transfusion reactions in outpatients receiving leukocyte-reduced blood components.
2. History of multiple transfusions and previous transfusion reactions may be negatively or positively associated with the risk of transfusion reactions in outpatients, even in the era of leukocyte-reduced blood products.

INTRODUCTION

Transfusion is a life-saving procedure, especially in certain clinical conditions, including massive bleeding, anaemia and coagulopathies. Adverse effects, ranging from minor discomforts to life-threatening reactions, may occur during or after transfusion. Among them, transfusion-transmitted infection (TTI) was first reported in the 1940s, and although improvements have been achieved, a risk of 0.1%–1% of TTI for those who received transfusion therapy in certain regions persists [1]. In recent years, the incidence of TTI decreased drastically due to comprehensive screening tests of pathogens in the donor blood. Subsequently, another two transfusion-associated adverse reactions (TAARs), febrile non-haemolytic transfusion reactions (FNHTRs) and minor allergic reactions (MARs), have remained the most common for nearly one century [2]. With the advancement of technologies, the underlying mechanisms of TAARs had been explored, and certain interventions have been applied to prevent or alleviate TAARs. For instance, it was proposed that proinflammatory cytokines produced by leukocytes during the storage of blood products are the main cause of FNHTRs [3, 4]. Thereafter, accumulating evidence revealed that FNHTRs were associated with these leukocyte-released cytokines like tumour necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, IL-8 and soluble CD40 ligand [5–9]. Besides, previous studies revealed that the frequency of FNHTRs or other immunologic reactions could be reduced when fresh, washed or leukocyte-reduced blood components were transfused [10–12], which could be associated with a decreased level of cytokines in the blood units [13]. However, considering the cost-effectiveness of transfusion intervention, washed blood products were usually given to those who experienced adverse reactions two and more times, although premedication was given or one episode of serious side effects in previous transfusions [14].

The rate of TAARs varies due to different ethnicities, study populations, institutions, regions, surveillance systems of TAARs and/or the existence of haemovigilance. Nevertheless, the literature reviews indicated that the overall incidence of TAARs (1.47% per unit) in Japan [15] was much higher than that in the United States (0.24% per unit) [16]. Hence, standard pre-administration of various agents was given to prevent TAARs in clinical practice, as the occurrence could affect the therapeutic strategies in both outpatients and inpatients. The rate of transfusion premedication also varies in different countries and institutions, with an estimated frequency of 8.5%–80% [17, 18]. Previously, one meta-analysis showed that there was no benefit of premedication using acetaminophen and antihistamine for FNHTRs and MARs, respectively [19, 20]. However, this conclusion was based on four clinical trials with moderate quality [20–23]. Hence, the indications and use of transfusion premedication remain controversial, especially in the era of leukocyte-reduced blood products.

To realize the overall incidence of TAARs and the premedication rate before transfusion in Taiwanese, we designed this study to evaluate whether there was a relationship in the frequency of TAARs with the administration of transfusion premedication in the outpatients receiving leukocyte-reduced blood components. We also aimed to investigate whether the introduction of an educational programme could improve the understanding of physicians related to the unnecessary use of premedication and if this could elicit changes in their prescribing activities and the occurrence of TAARs in outpatients receiving transfusion therapy with leukocyte-reduced blood products.

MATERIALS AND METHODS

Study design

This is a retrospective study that included outpatients who received blood component transfusions from April 2017 to October 2018 in Far Eastern Memorial Hospital (FEMH). Data were retrieved from the records of outpatients who received transfusion therapy during the study interval. The clinical data, including patient age, gender, predisposing diseases (including solid cancers, haematological cancers, renal

diseases and other benign/idiopathic anaemia/thrombocytopenia), the speciality of the physician who prescribed transfusion therapy, histories of transfusion events and TAARs, category of transfused blood components (including leukocyte-reduced packed red cell components or platelet/plasma products), the medication (including antipyretics, antihistamine and steroids) given prior to transfusion and the TAARs events, were collected via electronic medical record. Besides, the educational programme on evidence-based transfusion was provided in the period December 2017 to February 2018 to educate physicians related to the unnecessary use of premedication. Briefly, physicians were made aware that accumulating evidence has revealed that premedication did not affect the occurrence of TAARs, and hence, it seemed that there was no need to give premedication to patients with no history of TAARs; while premedication could be considered to be acceptable for patients with mild TAARs if there were restrictions on the use of washed blood products. Debriefing sessions, in which the premedication rate and events of TAARs were mainly included, had been announced quarterly for clinicians who prescribed transfusion therapy in the outpatients since December 2017. This study was conducted in compliance with the Declaration of Helsinki 1964 and was approved by the institutional review board of FEMH (108053-E).

Evaluation of transfusion reactions

The events of TAARs were verified by at least two blood bank physicians, according to National Healthcare Safety Network (NHSN) biovigilance component protocol guidelines, version 2.2 [24]. For instance, patients with elevated body temperature to values higher than 38°C, with changes greater than 1°C from the baseline temperature, or chills during or no more than 4 h after transfusion were regarded as FNHTR. On the other hand, patients who developed two or more of the following symptoms, including conjunctival oedema, oedema of lips, tongue and/or uvula, erythema and oedema of the periorbital area, generalized flushing, hypotension, localized angioedema, maculopapular rash, pruritus, respiratory distress, bronchospasm and urticaria during or no more than 4 h after transfusion, were regarded as allergic. Those outpatients who were reported to have symptoms and signs but did not meet the criteria were considered as inconsistent with TAARs. All reported cases of TAARs were reviewed and verified by at least two blood bank physicians.

Statistical analysis

The analysis of data was conducted by SPSS (version 19.0; SPSS Inc., Chicago, IL). The descriptive data were presented as the mean ± standard deviation or number (in percentage). Univariate analysis was performed to evaluate the association of risk factors and events of TAARs using the Mann–Whitney *U* test or Kruskal–Wallis test for the continuous data or chi-square test with Pearson's correlation or Fisher's exact probability test for the categorical data. Multivariate binary logistic regression models were then analysed for adjusting confounding factors. The results were expressed by the odd ratio (OR) with a 95% confidence interval (95% CI). A *p*-value smaller than 0.05 was considered statistically significant.

RESULTS

From April 2017 to October 2018, a total of 5018 blood units were transfused to 803 outpatients, with 2493 transfusion events reported. Of the blood components, the most frequently transfused component was leukocyte-reduced packed red cells ($n = 4338$), followed by leukocyte-reduced apheresis platelets ($n = 540$), fresh frozen plasma ($n = 78$), washed packed red cells ($n = 36$), cryoprecipitate ($n = 22$), apheresis platelets ($n = 2$) and frozen plasma ($n = 2$). Washed platelets were unavailable in Taiwan. As shown in Table 1, the mean age was 63.1 ± 15.7 years, and among the 803 outpatients, 446 were female. Transfusion was prescribed and given to the outpatients with solid cancers (40.3%, $n = 324$), haematological cancers (15.9%, $n = 128$), renal diseases (18.6%, $n = 149$) and other benign/idiopathic anaemia/thrombocytopenia (25.2%, $n = 202$) after the evaluation by clinicians. Among them, transfusions were mostly prescribed by the haematologist-oncologist (79.7%, $n = 1986$), followed by the nephrologist (9.9%, $n = 246$) and gynaecologist (5.0%, $n = 125$) by events. According to the number of transfusions, 290 events (11.6%) were first-time transfusions, 493 events (19.8%) were second to fourth transfusions, while 1708 (68.8%) were fifth or more transfusions.

TABLE 1 The demographic data in the outpatients receiving transfusion therapy

Variables	Values
Age (years)	63 ± 15.7
Gender (male/female)	357/446
Predisposing disease	
Solid cancers	324 (40.3%)
Haematological cancers	128 (15.9%)
Renal diseases	149 (18.6%)
Other benign anaemia/thrombocytopenia	202 (25.2%)
The specialty of clinical prescribing transfusion by events	
Haemato-oncologist	1986 (79.7%)
Nephrologist	246 (9.9%)
Gynaecologist	125 (5.0%)
Others	134 (5.4%)
Patient history of transfusion events	
1 time	290 (11.6%)
2–4 times	493 (19.8%)
5 times and more	1708 (68.6%)
Patient history of TAARs by events	335 (13.4%)

Note: Data were expressed in the mean ± standard deviation or number (in percentage).
Abbreviation: TAARs, transfusion-associated adverse reactions.

Additionally, 335 events (13.4%) were transfusions to patients with history of TAARs.

The overall premedication rate was 84.1% in the outpatients during the study interval, including the use of antipyretics (14.3%), antihistamines (56.0%) and steroids (37.6%). The most commonly used regimen of premedication was diphenhydramine only (51.7%), followed by the steroids only (44.7%) and acetaminophen plus diphenhydramine (14.9%). The overall premedication rates before and after the educational programme were 92.4% (1085 had premedication in 1174 events) and 76.7% (1011 had premedication in 1319 events) by events, respectively. In patients who had solid cancers, the premedication rates before and after the educational programme were 90.7% (303 among 334 events) and 83.6% (392 among 469 events), respectively. For patients with haematological cancers, the premedication rates before and after the educational programme were 97.1% (407 among 419 events) and 81.0% (312 among 385 cases), respectively. In patients with renal disorders, they were 80.3% (163 among 203 events) and 44.4% (80 among 180 events), respectively. For those with other benign anaemia/thrombocytopenia, they were 97.2% (212 among 218 events) and 79.6% (227 among 285 events), respectively.

In the study interval, 28 events of TAARs were reported and confirmed, including 10 FNHTRs and 18 MARs. Among these, one FNHTR and four MARs did not have premedication before transfusion; three of them thereafter received premedication for subsequent transfusion therapy, and two of them did not have a subsequent transfusion. As shown in Table 2, TAARs were commonly seen in patient with solid and haematological cancers, receiving transfusion therapy for the first time and receiving platelets/plasma and/or red cell products. Besides, those who were administered acetaminophen only had the higher occurrence of MARs in comparison with other groups who received alternative premedication or had no premedication during or after transfusion.

Before the educational programme, univariate analysis revealed that the administration of premedication had limited effect in preventing TAARs in outpatients receiving transfusion therapy in the period April to December 2017 (OR: 0.82, 95% CI: 0.101–6.52). Hence, the educational programme of evidence-based transfusion was provided in the period December 2017 to February 2018, followed by quarterly session debriefs. As shown in Figure 1, the premedication rate was 92.4% before the educational programme and significantly decreased

TABLE 2 The clinical features of TAARs in predisposing diseases, transfused blood components and type of premedication in the outpatients receiving transfusion therapy

	TAARs per event		
Variables	**All TAARs/total events**	**FNHTRs**	**MARs**
Predisposing disease			
Solid cancers	11/803 (1.4%)	2 (0.3%)	9 (1.1%)
Haematological cancers	13/803 (1.6%)	6 (0.7%)	7 (0.9%)
Renal diseases	2/383 (0.5%)	1 (0.3%)	1 (0.3%)
Other benign anaemia/thrombocytopenia	1/502 (0.2%)	1 (0.2%)	0 (0.0%)
Patient history of transfusion events			
1 time	5/290 (1.7%)	0 (0.0%)	5 (1.7%)
2–4 times	6/493 (1.2%)	1 (0.2%)	5 (1.0%)
5 times and more	17/1708 (1.0%)	9 (0.5%)	8 (0.5%)
Transfused blood components			
Red cells only	16/2051 (0.8%)	5 (0.2%)	11 (0.6%)
Platelets/plasma only	6/246 (2.4%)	2 (0.8%)	4 (1.6%)
Both red cells and platelets/plasma	6/194 (3.1%)	3 (1.5%)	3 (1.5%)
Premedication			
None	5/397 (1.3%)	1 (0.3%)	4 (1.0%)
Acetaminophen only	1/31 (3.2%)	0 (0.0%)	1 (3.2%)
Diphenhydramine only	10/866 (1.2%)	8 (0.9%)	2 (0.2%)
Steroids only	8/657 (1.2%)	0 (0.0%)	8 (1.2%)
Acetaminophen plus diphenhydramine	0/261 (0.0%)	0 (0.0%)	0 (0.0%)
Acetaminophen plus steroids	0/11 (0.0%)	0 (0.0%)	0 (0.0%)
Diphenhydramine plus steroids	4/216 (1.9%)	1 (0.5%)	3 (1.4%)
Acetaminophen plus diphenhydramine plus steroids	0/52 (0.0%)	0 (0.0%)	0 (0.0%)

Note: Data were expressed in number (in percentage).
Abbreviations: FNHTRs, febrile non-haemolytic transfusion reactions; MARs, minor allergic reactions; TAARs, transfusion-associated adverse reactions.

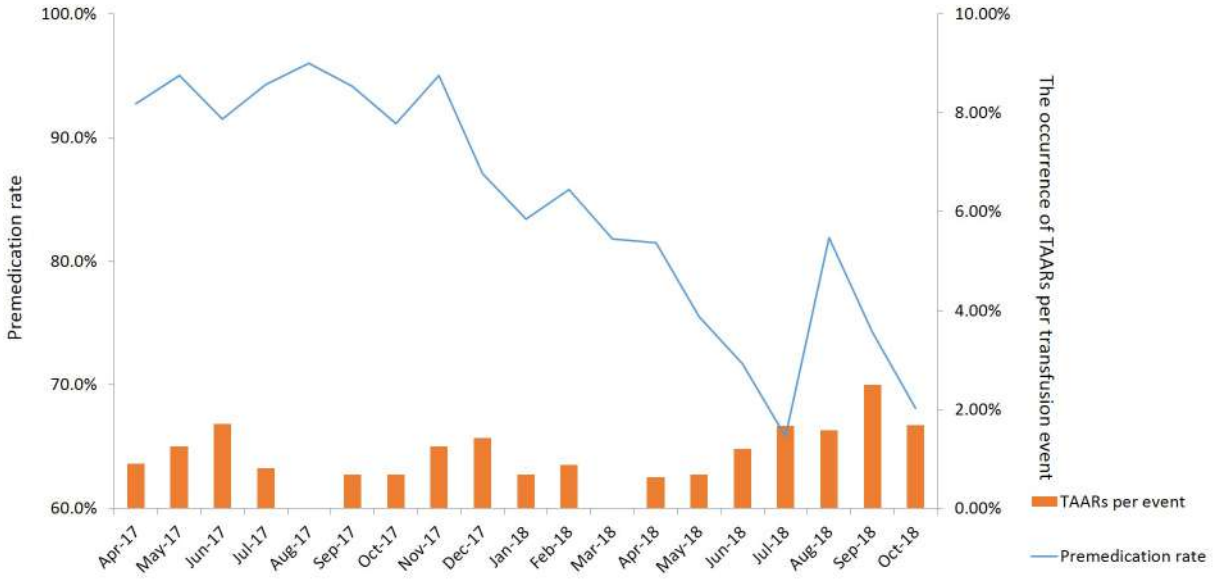

FIGURE 1 The premedication rate and occurrence of TAARs per transfusion event in the outpatients. The overall premedication rate was 84.1% and 28 events with TAARs were reported and verified, including 10 FNHTRs and 18 minor allergic reactions during the study interval. The premedication rate was 92.4% before educational program (April to December, 2017), and had been significantly decreased to 76.7% after educational program and quarterly session debriefs since 2018 ($p < 0.001$). Besides, there was limited change of the occurrence of TAARs per transfusion event between the episodes before and after educational program (1.11% vs. 1.14%, $p = 0.964$). TAARs, transfusion-associated adverse reactions

to 76.7% after the educational programme, followed by session debriefs in 2018 ($p < 0.001$). Importantly, it seemed that the occurrence of TAARs per transfusion event was almost unchanged in the post-educational period compared to the pre-educational one (1.11% vs. 1.14%, $p = 0.964$). Among them, FNHTRs significantly decreased after the educational programme (0.68% vs. 0.15%, $p = 0.045$); while a slight increase of MARs was observed after the programme, but with no statistical significance (0.43% vs. 0.99% per transfusion event, $p = 0.093$).

To evaluate whether the occurrence of TAARs in outpatients was associated with the category of predisposing diseases, transfused blood components, previous histories of transfusion therapy and TAARs, and the use or not of premedication, univariate analysis was performed. It revealed that previous history of TAARs ($p < 0.001$) and transfusion of platelet/plasma with or without red cells ($p = 0.002$) were significantly associated with TAARs. Instead, there was no remarkable relationship between age ($p = 0.922$), gender ($p = 0.250$), predisposing diseases ($p = 0.120$), patient history of transfusion events ($p = 0.540$), premedication ($p = 0.775$) and occurrence of TAARs. Multivariate logistic regression analysis was further performed. In the regression model, patient age, gender and the factors mentioned above were adjusted as confounding factors to evaluate the associations of TAARs occurrence with the dependent variables. As shown in Table 3, the history of TAARs in previous transfusions was significantly associated with the occurrence of TAARs during or after transfusion (OR: 3.72, 95% CI: 1.34–10.35, $p = 0.012$). Besides, outpatients with a history of multiple transfusions of five times and more were inversely associated with TAARs occurrence (OR: 0.25, 95% CI: 0.08–0.80, $p = 0.020$). There was no association of premedication with occurrence of TAARs (OR: 0.56, 95% CI: 0.20–1.58, $p = 0.276$). The results revealed that overall, decreased use of

TABLE 3 Multivariate binary logistic analysis on the association of clinical features with TAARs in the outpatients receiving transfusion therapy

	Multivariate analysis	
Variables	**OR (95% CI)**	***p* value**
Age of 65 years and more	1.19 (0.54–2.63)	0.670
Female gender	0.58 (0.26–1.27)	0.171
Predisposing disease (compared with other benign anaemia/thrombocytopenia)		
Solid cancers	3.78 (0.81–17.68)	0.091
Haematological cancers	3.56 (0.69–18.37)	0.130
Renal diseases	1.47 (0.20–10.80)	0.708
Patient history of transfusion events (compared with the first time)		
2–4 times	0.51 (0.15–1.72)	0.275
5 times and more	0.25 (0.08–0.80)	0.020
Patient history of TAARs	3.72 (1.34–10.35)	0.012
Transfused blood components (compared with red cells only)		
Platelets/plasma only	2.14 (0.72–6.35)	0.172
Both red cells and platelets/plasma	2.55 (0.76–8.59)	0.130
Premedication	0.56 (0.20–1.58)	0.276

Note: Data were expressed in OR (95% CI).
Abbreviations: CI, confidence interval; OR, odds ratio; TAARs, transfusion-associated adverse reactions.

premedication did not result in increased incidence of TAARs in outpatients.

DISCUSSION

In this study, our main finding was that the overall premedication rate in outpatients significantly decreased from 92.4% to 76.7% after the educational programme of evidence-based transfusion practice with multidisciplinary collaborations was implemented. Meanwhile, the reduction of the premedication rate did not affect the incidence of TAARs. History of TAARs in the previous transfusion seemed to be associated with TAARs occurrence; however, history of multiple transfusions was inversely associated with TAARs during or after transfusion. To the best of our knowledge, this is the first study investigating the association of premedication with the occurrence of TAARs in the outpatients in the Taiwanese population.

The use of transfusion premedication remains controversial. Previous studies [17–23, 25, 26] have shown that premedication did not prevent TAARs such as FNHTRs and MARs, which is generally consistent with our results. One prospective randomized clinical trial revealed that administration of 500 mg acetaminophen or 25 mg diphenhydramine or placebo prior to transfusion did not significantly affect occurrence of TAARs, when leukocyte-reduced blood components were transfused, although a slight but not significant reduction of FNHTRs ($p = 0.08$, one-sided p-value) was observed [20]. Another prospective study conducted in five university teaching hospitals also revealed that premedication had little effect on the occurrence of TAARs in platelet transfusions [26]. Interestingly, there were three phases in this investigation, including non-standardized transfusion practice in the first phase, the introduction of standardized premedication protocol in transfusion practice in the second phase and standardized premedication protocol accompanied with prestorage leukocyte-reduced platelet transfusion in the third phase. It was revealed that the use of leukocyte-reduced platelet components, rather than premedication, significantly decreased the occurrence of TAARs [26]. As the universal use of prestorage leukocyte-reduced red cell components has been introduced in our hospital since 2016, the previous data revealed a significant decrease in the incidence of all TAARs (0.33% vs. 0.23%, $p < 0.001$), FNHTRs (0.24% vs. 0.13%, $p < 0.001$) and respiratory transfusion-related reactions (0.03% vs. 0.01%, $p = 0.010$). However, there was no significant change in MARs before and after introduction of the programme (0.07% vs. 0.09%, $p = 0.286$). These findings were compatible with the previous studies showing that the incidence of FNHTRs, but not MARs, was significantly reduced after conversion to universal prestorage leukoreduction in transfused blood components [27, 28]. Furthermore, only two platelet components without prestorage leukoreduction out of 540 in this study interval were transfused to outpatients. We subsequently observed that pre-storage leukoreduced blood components, instead of premedication, play a vital role in the prevention of TAARs.

The rate of transfusion premedication varied in different countries and institutions [17]. In a large-scale hospital in the United States, premedication was used in approximately 80% of adult patients [29], while it was used in 68% of oncology patients in a children's hospital [30]. In tertiary centres in Canada, it was reported to be 73% [26], but interestingly, the premedication rate decreased to 50% after implementation of standardized premedication guidelines. Additionally, a nationwide questionnaire survey in Japan [31] revealed that premedication was given at 5.1% of institutions for red cell transfusions, 21.2% for platelet transfusions and 10.9% for plasma transfusions as primary prophylaxis in patients with haematological diseases; while secondary prophylaxis was given at 62.6% of institutions for red cell transfusions, 87.3% for platelet transfusions and 73% for plasma transfusions. Past history of transfusion and TAARs were found as important factors in determining the indication of premedication by physicians, and premedication should be considered separately in primary and secondary prophylaxis. Accordingly, a standardized and evidence-based premedication protocol should be developed and implemented for patients receiving transfusions in the institution.

Drug toxicity is another consideration for transfusion premedication in outpatients. In the literature review, acetaminophen and diphenhydramine have been the two most commonly used medications in the pre-transfusion prevention of TAARs. In general, acetaminophen was considered to be a safe agent, but an overdose of acetaminophen could induce hepatotoxicity, especially in those with chronic heavy alcohol consumption, predisposing liver diseases or use of enzyme-inducing drugs [32, 33]. Importantly, acetaminophen may also mask initial fever from septic transfusion reactions or transfusion-unrelated etiologies in patients with comorbidities such as cancer [18]. Furthermore, diphenhydramine could cause sedation and urinary retention because of its anticholinergic effect. It was reported that administration of 50-mg diphenhydramine in one dose could even lead to impairment of memory, mood and psychomotor performance when driving vehicles, which could thus influence outpatient safety [34, 35]. Hence, premedication for the prevention of TAARs should be cautiously evaluated, particularly in outpatients.

In addition to transfusion premedication, it is important to identify whether there are established risk factors leading to the occurrence of TAARs. It was reported that the frequency of TAARs associated with transfusion of red cells and plasma products in first transfusion episodes was significantly higher than that in subsequent transfusion episodes, and a similar trend in platelet transfusion was also observed but without statistical significance [36]. These findings were consistent with our results in which the outpatients receiving multiple transfusions (of five times and more) had a significantly lower risk of experiencing TAARs when compared with those receiving the first transfusion. However, it was also reported that the number of platelet transfusions with photochemical treatment limitedly affected the risk of developing TAARs [37]. Whether the number of transfusions contributed to the development of TAARs could be affected by a variety of factors, including the processing of blood components, region, ethnicity, study population, predisposing diseases of the transfused patient and so on. Besides, it was reported that patients with a history of FNHTRs had an approximately 15% risk of developing recurrent TAARs [38]. In our study, 10 (2.99%) out of 355 outpatients

with a history of TAARs developed recurrent TAARs (OR: 3.66, 95% CI: 1.67–7.99, $p < 0.001$). Subsequently, we observed that the outpatients who experienced TAARs in the previous transfusion had a significantly higher risk of developing recurrent TAARs.

There were several limitations in this study. First, this is a retrospective study design conducted in a single institution. Besides, the premedication rate was reduced to merely 76.7% after an educational programme in the 10-month interval as the premedication behaviours of the patients and healthcare providers were somewhat difficult to be changed in such a short period. The study population was also limited to only outpatients in our survey; hence, the results could be partially inconsistent with the previous studies, which included inpatients and outpatients. Nevertheless, it has sometimes been difficult to define an event of TAARs among the inpatients. As a result, the incidence of TAARs could be presented per transfused event or per transfused unit, leading to inconsistencies among the previous investigations. Also, some unknown risk factors related to TAARs could be missed in the chart review, such as the length of storage of blood components transfused to the outpatients. Therefore, these variables were not analysed in the study. Furthermore, most blood products evaluated in our study were packed red cells, which had a different frequency and type of TAARs in comparison with platelets and plasma products; however, our results showed that there was no statistical significance of TAARs occurrence in patients receiving platelets/plasma transfusion compared with red cells. Finally, the incidence of TAARs could have been underestimated, although the haemovigiliance system has been well established in FEMH. In our hospital, for example, extensive education programmes related to transfusion medicine and haemovigiliance were provided to physicians and nurses at least two times per year. There were 585 events of suspected TAARs reported among the 90,072 transfusion events, with 223,336 transfused blood units in the period 2017–2019. Furthermore, the Taiwan haemovigilance network has been established by the Taiwan society of blood transfusion (TSBT) and Taiwan blood services foundation (TBSF) with hospital accreditations to enhance transfusion quality and patient safety since 2017. In 2019, at least 33 hospitals participated in the Taiwan haemovigilance network, including 13 medical centres. Despite the efforts to haemovigilance, however, the incidence of TAARs could be somewhat inevitably underestimated.

In conclusion, we found that decreased use of premedication is not associated with increased incidence of TAARs in outpatients receiving leukocyte-reduced blood components. Thus, our present results provide substantial evidence of the need to revise the clinical practice in the era of leukocyte-reduced blood products. Besides, a history of TAARs in the previous transfusion may be associated with a higher risk of developing TAARs during or after the transfusion, while multiple transfusions may be associated with a lower risk of TAARs in outpatients.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ORCID

Chih-Chun Chang https://orcid.org/0000-0002-4377-7026

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ORIGINAL ARTICLE

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Platelet transfusion and mortality in patients with sepsis-induced thrombocytopenia: A propensity score matching analysis

Shanshan Wu[1] | Qin Chen[2] | Jingye Pan[2] | Aiming Zhou[2]

[1]Medical Research Center, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China

[2]Department of Intensive Care Unit, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China

Correspondence
Aiming Zhou, Department of Intensive Care Unit, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang 325000, China.
Email: zhouaiming@wzhospital.cn

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Abstract

Background and Objectives: Thrombocytopenia is common among sepsis patients. Platelet transfusions are frequently administered to increase platelet counts, but their clinical impacts remain unclear in sepsis-induced thrombocytopenia. The goal of this study was to explore the association between platelet transfusion and mortality in patients with sepsis-induced thrombocytopenia.

Materials and Methods: The study was based on the Medical Information Mart for Intensive Care (MIMIC) III database. Septic patients with severe thrombocytopenia (a platelet count ≤ 50/nl) were included in the study and were divided into two groups: a platelet transfusion group (PT group) and a no platelet transfusion group (NPT group). The primary outcome was in-hospital mortality, and the secondary outcomes were the length of intensive care unit (ICU) stay (LOS-ICU) and 90-day mortality. Propensity score matching multivariable logistic regression was used to reduce the imbalance.

Results: A total of 1733 patients were included: 296 patients were included in the PT group and 1437 patients were included in the NPT group. After propensity score matching, 296 paired patients constituted each group. Crude hospital mortality was significantly higher in the PT group than in the NPT group (145 [48.99%] vs. 567 [39.46%], $p = 0.002$). In the extended multivariable logistic models for hospital mortality, the odds ratio (OR) of receiving a platelet transfusion was consistently significant in all six models (OR range, 1.340–1.525, $p < 0.05$ for all). In the following subgroups, platelet transfusion was associated with increased in-hospital mortality: age > 60 years; sex: female; sequential organ failure assessment score ≤8; simplified acute physiology score ≤ 47; platelet count >29/nl and the complication of congestive heart failure. However, there were no significant differences in the 90-day mortality rate (170 [57.43%] vs. 741 [51.57%], $p = 0.066$) or the LOS-ICU (5.84 [2.68–11.78] vs. 4.94 [2.18–12.72], $p = 0.442$) between the two groups. All these results remained stable after adjustment for confounders and in the comparisons after propensity score matching.

Conclusions: The propensity score-matched analysis showed that platelet transfusion was associated with increased in-hospital mortality in septic patients with severe thrombocytopenia (a platelet count ≤ 50/nl). However, it was not associated with 90-day mortality or the length of ICU stay.

Keywords
90-day, mortality, platelet transfusion, propensity score matching, sepsis-induced thrombocytopenia

Highlights

- Platelet transfusion was associated with increased in-hospital mortality in septic patients with severe thrombocytopenia (a platelet count ≤50/nl).
- With regard to age (>60 years), sex (female), sequential organ failure assessment score (≤8), simplified acute physiology score (≤47), platelet count (>29) and comorbidities (congestive heart failure), subgroup analyses showed that platelet transfusion was associated with increased in-hospital mortality.
- Patients with sepsis-induced thrombocytopenia might not benefit from platelet transfusion regarding 90-day mortality or length of intensive care unit stay.

INTRODUCTION

Sepsis is the most common disease in the intensive care unit (ICU), defined as a life-threatening syndrome of organ dysfunction caused by a dysregulated host response to severe infection [1], and it has been considered a major cause of health loss worldwide. According to a recent scientific publication, there were approximately 48.9 million cases and 11 million sepsis-related deaths worldwide in 2017, which accounted for almost 20% of all global deaths [2].

Clinically, a decrease in platelet count is common among patients with sepsis who are admitted to the ICU. The incidence of sepsis-induced thrombocytopenia is approximately 25% on ICU admission [3] and approximately 55% during the hospital stay [4]. Studies have confirmed that platelets play a crucial role in the inflammatory balance, immune responses, tissue repair, and regeneration, in addition to their important role in haemostasis and thrombosis [5–7]. Based on recent studies, thrombocytopenia is closely associated with multiple organ dysfunction syndromes, prolonged ICU stay and high mortality in sepsis patients [8]. In addition, thrombocytopenia is an early prognostic marker for septic shock onset in ICU patients in the first 24 h [9]. Nonresolution of thrombocytopenia is associated with increased 28-day mortality in this population [3].

In general, the recovery of thrombocytopenia in septic patients is always accompanied by the control of infection and improvement of the patient's condition. Recently, several studies have explored the impact of platelet-elevating drugs (recombinant human thrombopoietin, rhTPO) on sepsis-induced thrombocytopenia, which showed that rhTPO could lead to the quick recovery of the platelet count and improve the prognosis of patients with severe sepsis-induced thrombocytopenia [10–12]. Platelet transfusions are the most common clinical therapy to increase platelet counts. However, platelet transfusion is limited in clinical practice and does not have a precise indication in sepsis patients [13, 14]. There are no large prospective clinical trials exploring the impact of platelet transfusion on sepsis-induced thrombocytopenia. Two of the main challenges with performing a randomized controlled trial are (1) challenges in recruiting participants from this relatively uncommon and acutely ill patient group and (2) obtaining buy-in from clinicians.

A recent large registry study showed that platelet transfusion was not associated with an increased risk of death in critically ill patients [15]. Nonetheless, there is no large study based on platelet transfusion in severe sepsis-induced thrombocytopenia investigating whether platelet administration influences the prognosis of sepsis patients. In this study, we aimed to determine the potential association between platelet transfusion and clinical outcomes in sepsis patients. We hypothesized that platelet transfusions in this population are associated with worse clinical outcomes, including in-hospital mortality, 90-day mortality and length of ICU stay.

METHODS

Database

This was a retrospective study based on the online international Medical Information Mart for Intensive Care III (MIMIC III) database [16]. The MIMIC III database is a large, single-centre database comprising information related to patients admitted to the critical care units at the Beth Israel Deaconess Medical Center, which is a fully integrated medical centre that provides adult care, with over 1250 full-time medical staff managing more than a half a million outpatient visits each year. The database contains information for 46,520 patients admitted to the critical care units between 2001 and 2012. All the patients included in the database were deidentified, and the need for informed consent was waived. One author (A.Z.) obtained access to this database (certification number 35752875) and was responsible for data extraction.

Study population and definitions

Septic patients with a platelet count level ≤ 50/nl were eligible for inclusion in our study. Sepsis was defined according to the third

sepsis definition [1], which was defined as a suspected infection and an acute change in patients with a total sequential organ failure assessment (SOFA) score ≥2 points. For patients who were readmitted to the ICU, only data from the first ICU admission were included. Patients younger than 18 years or older than 89 years were excluded. The primary outcome was in-hospital mortality. The secondary outcomes were 90-day mortality and the length of ICU stay (LOS-ICU).

Propensity score matching

Propensity score matching (PSM) was used to minimize the imbalance of the confounding factors between the PT and no platelet transfusion (NPT) groups. A one-to-one nearest neighbour matching algorithm was applied with a calliper width of 0.05 in our study. The following variables were selected to generate the propensity score: age, sex, SOFA score, simplified acute physiology score II (SAPS II), platelet count, diabetes mellitus, hypertension, chronic pulmonary disease, congestive heart failure, cancer, obesity, anaemia, haemorrhage, minimum haemoglobin (Hb_min) and maximum activated partial thromboplastin time (APTT_max).

The management of missing data

Variables with missing data are common in the MIMIC III database. For C-reactive protein, serum lactate, albumin and procalcitonin values, more than 20% were missing and were removed from this analysis. For other continuous variables with missing values less than 5%, the missing values were replaced by the mean or median values.

Statistical analysis

Continuous variables are depicted as medians with interquartile ranges. Student's *t*-test, analysis of variance, the Wilcoxon rank-sum test or the Kruskal–Wallis test was used as appropriate. Categorical data are shown as frequencies and proportions, and they were compared using the χ^2 test. The association between platelet transfusion and in-hospital mortality was determined by logistic regression, including the baseline as a covariate and the group as a fixed factor. An extended logistic model approach was used for adjusting the following covariates, and subgroup analysis was performed as described above: platelet count, age, sex, SOFA score, SAPS II score, comorbidities (chronic pulmonary disease, congestive heart failure and anaemia) and minimum haemoglobin (Hb_min). The survival outcome comparisons between the groups were analysed by the log-rank test. PSM was used to minimize the imbalance between groups. A two-tailed test was performed, and $p < 0.05$ was considered to indicate statistical significance. All statistical analyses were performed using the R package (version 3.6.3).

Ethics statement

The use of the MIMIC III database was approved by the Massachusetts Institute of Technology (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston, MA), and consent was obtained for the original data collection. Therefore, the ethical approval statement and informed consent were waived for this manuscript.

RESULTS

Baseline characteristics

The data of 1733 patients were included. The flow chart of patient selection is presented in Figure 1. The overall 90-day mortality rate was 52.6%. The comparisons of the baseline characteristics are listed in Table 1. Patients in the PT group were younger than those in the NPT

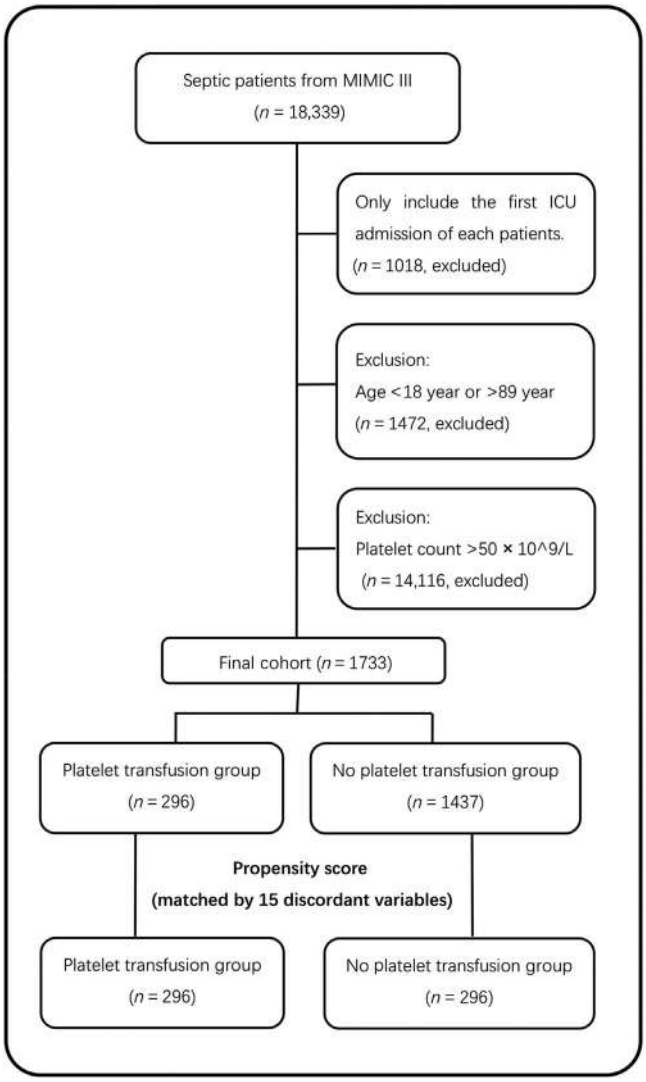

FIGURE 1 Flow chart of patient selection from the MIMIC III database

TABLE 1 Comparisons of the baseline characteristics between patients with and without platelet transfusion

Variables	No platelet transfusion ($n = 1437$)	Platelet transfusion ($n = 296$)	p-value
Age (years), median (IQR)	61.66 (51.00–72.79)	57.16 (48.49–68.92)	0.001*
Male, *n* (%)	784 (54.56)	168 (56.76)	0.489
Comorbidities, *n* (%)			
Diabetes mellitus	311 (21.64)	71 (23.99)	0.376
Hypertension	199 (13.85)	44 (14.86)	0.646
Chronic pulmonary	239 (16.63)	29 (9.80)	0.003*
Congestive heart failure	311 (21.64)	87 (29.39)	0.004*
Cancer	225 (15.66)	44 (14.86)	0.732
Obesity	65 (4.52)	8 (2.70)	0.156
Anaemia	179 (12.46)	53 (17.91)	0.012*
Haemorrhage	29 (2.02)	11 (3.72)	0.076
Disease severity scores, median (IQR)			
SOFA score on ICU admission	8.00 (6.00–11.00)	8.00 (6.00–11.00)	0.806
SAPS II on ICU admission	47.00 (37.00–57.00)	46.00 (37.00–55.00)	0.534
Biochemical indices, median (IQR)			
Platelet count	31.00 (19.00–41,00)	20.00 (11.00–33.00)	<0.001*
Hb_min	7.60 (6.80–8.40)	7.50 (6.80–8.03)	0.012*
PT_max	20.40 (16.20–28.90)	19.90 (16.10–27.15)	0.368
APTT_max	58.40 (38.90–115.50)	59.30 (38.70–150.00)	0.493
Clinical outcomes			
LOS-ICU (day), median (IQR)	4.94 (2.18–12.72)	5.84 (2.68–11.78)	0.442
In-hospital mortality, *n* (%)	567 (39.46)	145 (48.99)	0.002*
Mortality of 90 days, *n* (%)	741 (51.57)	170 (57.43)	0.066

Note: Values are shown as medians with interquartile ranges (IQRs) unless otherwise indicated. p values comparing platelet transfusion group (PT group) to no platelet transfusion group (NPT group).

Abbreviations: APTT_max, maximum of activated partial thromboplastin time; Hb_min, minimum of haemoglobin; ICU, intensive care unit; LOS-ICU, length of ICU stays; PT_max, maximum of prothrombin time; SAPS II, simplified acute physiology score II; SOFA, sequential organ failure assessment.

*$p < 0.05$.

group (57.16 [48.49–68.92] vs. 61.66 [51.00–72.79] years, $p = 0.001$). The platelet count was significantly lower in patients who received platelet transfusions (20.00 [11.00–33.00] vs. 31.00 [19.00–41.00], $p < 0.001$). The SOFA score on admission was similar in the PT group and the NPT group (8.00 [6.00–11.00] vs. 8.00 [6.00–11.00], $p = 0.806$). Patients in the PT group were more likely to have congestive heart failure (87 [29.39%] vs. 311 [21.64%], $p = 0.004$), while more patients in the NPT group were complicated with chronic pulmonary disease (29 [9.80%] vs. 239 [16.63%], $p = 0.003$). The hospital mortality rate was significantly higher in the PT group than in the NPT group (145 [48.99%] vs. 567 [39.46%], $p = 0.002$). However, there were no significant differences in the 90-day mortality rate (170 [57.43%] vs. 741 [51.57%], $p = 0.066$) or the LOS-ICU (5.84 [2.68–11.78] days vs. 4.94 [2.18–12.72] days, $p = 0.442$) between the PT group and NPT group.

Association between platelet transfusion and patient outcomes

The results of the univariable analysis showed that platelet transfusion was associated with higher in-hospital mortality (OR, 1.473; 95% CI, 1.146–1.894; $p = 0.002$). After the confounders (platelet count, SOFA score, SAPS II score, age, sex, comorbidities [chronic pulmonary disease, congestive heart failure, anaemia] and minimum haemoglobin [Hb_min]) were adjusted, platelet transfusion was also associated with hospital mortality (OR, 1.473; 95% CI, 1.113–1.948; $p = 0.007$) (Figure 2). In the extended multivariable logistic models (Table 2), we found that the OR of platelet transfusion was consistently significant in all six models (OR range, 1.340–1.525, $p < 0.05$ for all). Subgroup analysis was performed according to age, sex, SOFA score, SAPS II score, platelet count and congestive heart failure (Figure 2). In the subgroup analysis, platelet transfusion was significantly associated with increased mortality in patients with the following characteristics: age > 60 years (OR, 1.599; 95% CI, 1.055–2.422; $p = 0.027$), female sex (OR, 1.563; 95% CI, 1.022–2.391; $p = 0.040$), a SOFA score ≤8 (OR, 1.671; 95% CI, 1.138–2.454; $p = 0.009$), a SAPS II score ≤47 (OR, 1.585; 95% CI, 1.086–2.312; $p = 0.017$), a platelet count >29/nl (OR, 1.815; 95% CI, 1.108–2.971; $p = 0.018$), and the complication of congestive heart failure (OR, 1.599; 95% CI, 1.055–2.422; $p = 0.027$). However, there was no significant difference in survival at 90 days between the groups according to Kaplan–Meier survival estimates (Figure 3).

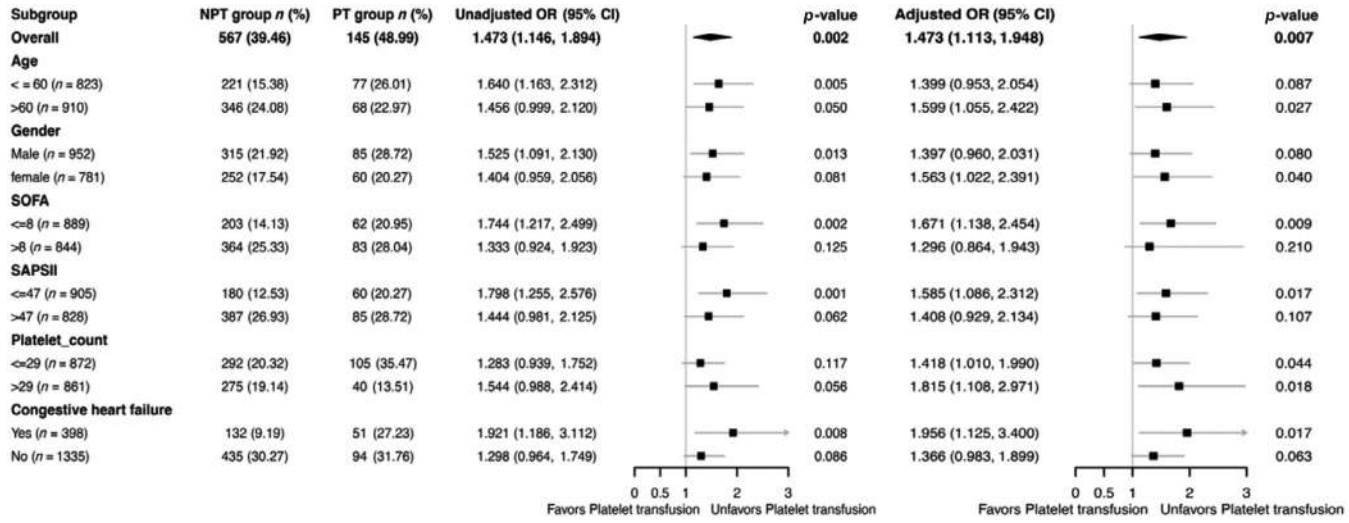

FIGURE 2 Subgroup analysis of the association between hospital mortality and platelet transfusion. CI, confidence interval; OR, odds ratio; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II

TABLE 2 Association between platelet transfusion and hospital mortality using an extended model approach

	Odds ratio of platelet transfusion	95% confidence interval	*p*-value
Model 1	1.473	(1.146–1.894)	0.002*
Model 2	1.340	(1.036–1.732)	0.026*
Model 3	1.397	(1077–1.811)	0.012*
Model 4	1.525	(1.156–2.012)	0.003*
Model 5	1.467	(1.109–1.941)	0.007*
Model 6	1.473	(1.113–1.948)	0.007*

Note: Adjusted covariates—Model 1 = platelet transfusion. Model 2 = Model 1 + (platelet count). Model 3 = Model 2 + (gender, age). Model 4 = Model 3 + (SOFA score, SAPSII score). Model 5 = Model 4 + (chronic pulmonary, congestive heart failure, anaemia). Model 6 = Model 5 + (Hb_min).
*$p < 0.05$.

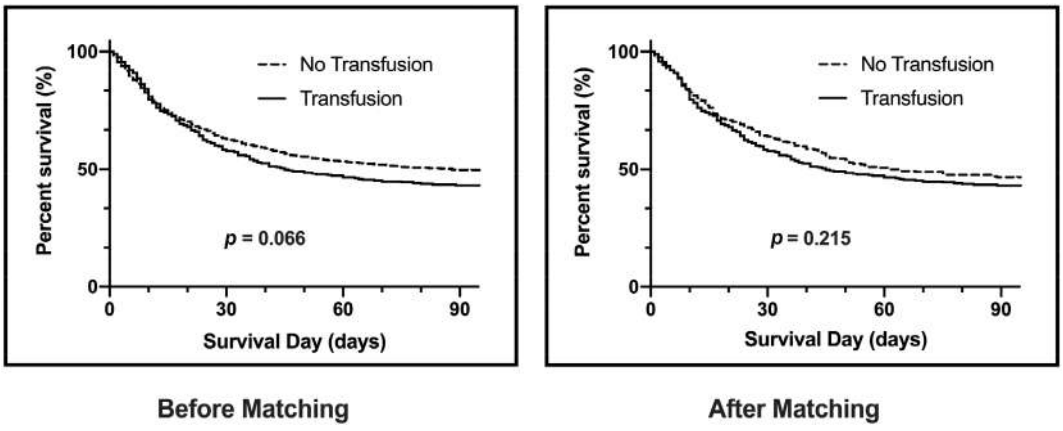

FIGURE 3 The 90-day survival curves of the platelet transfusion group (PT group) and no platelet transfusion group (NPT group)

Outcomes after propensity score matching

After PSM, 296 patients from each group were matched by a 1:1 matching algorithm (Table 3). For assessing the overall quality of the matched sample, the standardized difference of the means and the ratio of the variances between the propensity scores of both groups were compared, and the propensity scores between the groups were also inspected. There was no significant difference between the two matched groups with regard to any of the 15 covariates (age, sex, SOFA score, SAPS II score, platelet count, diabetes mellitus, hypertension, chronic pulmonary disease, congestive heart failure, cancer, obesity, Hb_min, APTT_max, anaemia and haemorrhage). Among the

TABLE 3 Comparisons of the covariates after propensity score matching

Variables	No platelet transfusion ($n = 296$)	Platelet transfusion ($n = 296$)	p-value
Age (years), median (IQR)	56.86 (45.21–67.63)	57.16 (48.49–68.92)	0.260
Male, *n* (%)	163 (55.07)	168 (56.76)	0.679
Comorbidities, *n* (%)			
Diabetes mellitus	57 (19.26)	71 (23.99)	0.162
Hypertension	30 (10.14)	44 (14.86)	0.082
Chronic pulmonary	19 (6.42)	29 (9.80)	0.132
Congestive heart failure	97 (32.77)	87 (29.39)	0.375
Cancer	41 (13.85)	44 (14.86)	0.725
Obesity	8 (2.70)	8 (2.70)	1.000
Anaemia	40 (13.51)	53 (17.91)	0.142
Haemorrhage	7 (2.36)	11 (3.72)	0.338
Disease severity scores, median (IQR)			
SOFA score on ICU admission	8.50 (6.00–11.00)	8.00 (6.00–11.00)	0.860
SAPS II on ICU admission	47.00 (36.00–56.25)	46.00 (37.00–55.00)	0.571
Biochemical indices, median (IQR)			
Platelet count	23.00 (13.00–35.00)	20.00 (11.00–33.00)	0.113
Hb_min	7.50 (6.80–8.30)	7.50 (6.80–8.03)	0.256
PT_max	19.05 (15.70–25.63)	19.90 (16.10–27.15)	0.118
APTT_max	59.95 (38.55–134.50)	59.30 (38.70–150.00)	0.702
Clinical outcomes			
LOS-ICU (day), median (IQR)	5.90 (2.35–14.70)	5.84 (2.68–11.78)	0.594
In-hospital mortality, *n* (%)	121 (40.88)	145 (48.99)	0.047*
Mortality of 90 days, *n* (%)	155 (52.36)	170 (57.43)	0.215

Abbreviations: APTT_max, maximum of activated partial thromboplastin time; Hb_min, minimum of haemoglobin; ICU, intensive care unit; LOS-ICU, length of ICU stays; PT_max, maximum of prothrombin time; SAPS II, simplified acute physiology score II; SOFA, sequential organ failure assessment.
*$p < 0.05$.

296 propensity-matched pairs, we found that the hospital mortality rate in the PT group was higher than that in the NPT group (145 [48.99%] vs. 121 [40.88%], $p = 0.047$). However, the 90-day mortality rate was not different between the groups (170 [57.43%] vs. 155 [52.36%], $p = 0.215$), and similar results were shown for LOS-ICU (5.84 [2.68–11.78] vs. 5.90 [2.35–14.70], $p = 0.594$) (Table 3).

DISCUSSION

The present study demonstrated that platelet transfusion was associated with increased in-hospital mortality in sepsis patients with severe thrombocytopenia. This result was robust in the PSM analysis after adjustment for covariates and remained consistent in the extended multivariable logistic models. Additionally, for patients with sepsis-induced thrombocytopenia, platelet transfusion was not associated with an increased risk of 90-day mortality or increased LOS-ICU. According to our findings, platelet transfusion was associated with worse clinical outcomes in sepsis patients with severe thrombocytopenia (a platelet count ≤50/nl).

According to previous research, nearly 35%–59% of patients with sepsis develop thrombocytopenia [17, 18], which has been recognized as an independent risk factor for mortality and a marker for disease severity [19]. The mechanisms of sepsis-induced thrombocytopenia are complex and probably correlate with various factors. For instance, endothelial dysfunction is a major consequence of sepsis and plays a crucial role in platelet activation and consumption [20]. This activation, which results in aggregation, is increased locally by cytokine production [21]. In addition, altered thrombopoiesis and/or haemophagocytosis are the major causes of thrombocytopenia, which is potentiated by sepsis mediators [22]. In addition, fluid resuscitation and surgical operation may influence platelet count.

Sepsis patients with platelet count less than 50/nl are considered to have sepsis-induced thrombocytopenia [23], which has high mortality and poor prognosis. It has been reported that the nonresolution of thrombocytopenia was associated with increased 28-day mortality instead of thrombocytopenia itself [3]. In our study, the in-hospital mortality rate was 41.08% and the 90-day mortality rate was 52.57%, which were higher than those in other studies [24]. A lower platelet count level (the median value was 29/nl) and a higher disease severity score (the median SOFA score value was 8 and the median SAPS II score value was 47) were the two main reasons for the high mortality rate in our study. Currently, there is no effective treatment for this condition. Infection control, organ support therapy, and immune

response regulation remain the mainstream treatments. In recent years, several studies have suggested that rhTPO could rapidly lead to a recovery of the platelet count, increase the number of survival days and reduce the 28-day mortality rate in sepsis patients with severe thrombocytopenia [10, 12]. Nevertheless, another study found that rhTPO was efficacious in increasing the patients' platelet counts, resulting in a shorter ICU stay (9.20 ± 5.38 vs. 10.88 ± 6.82 days, $p = 0.047$) for patients with severe thrombocytopenia and patients with severe sepsis, while there was no significant difference in 28-day mortality (rhTPO group: 25.0% vs. control group: 34.1%, $p = 0.158$) [25]. Therefore, the question of whether patients with sepsis-induced thrombocytopenia can benefit from rhTPO therapy still remains according to the controversial results.

Platelet transfusion is a regular clinical practice in thrombocytopenic patients for preventing and treating haemorrhages. Approximately 1,937,000 platelet component transfusions were given in the United States in 2017 [26]. Several pieces of evidence suggest that platelet transfusion is associated with adverse effects, such as infection [27]. Some experts believe that conventional platelet transfusion therapy may worsen patients' procoagulant and anticoagulant disorders. A prospective nonrandomized observational study revealed that prophylactic platelet transfusion was associated with an increased risk of thrombosis and mortality [28]. Another publication found that platelet transfusion was associated with higher risks of arterial thrombosis and mortality among thrombotic thrombocytopenic purpura (TTP) and heparin-induced thrombocytopenia (HIT) patients [29]. A cross-sectional study reported that platelet transfusion was associated with increased mortality and comorbidities in premature infants with thrombocytopenia [30]. In addition, platelet transfusion rates were associated with hospital mortality (adjusted relative risk per 5 ml/kg/d increase: 1.12; 95% CI 1.02–1.23, $p = 0.02$) among neonates receiving extracorporeal membrane oxygenation (ECMO) [31]. In our study, we found nearly the same results among sepsis patients with thrombocytopenia: platelet transfusion was associated with an increased risk of in-hospital mortality. This might have something to do with the influence of platelet transfusion that promotes the formation of microthrombi in sepsis patients and thus aggravates microcirculatory obstructions. Moreover, subgroup analysis revealed that platelet transfusion was significantly associated with increased mortality in patients with the following characteristics: age > 60 years, female sex, a SOFA score ≤8, a SAPS II score ≤ 47, a platelet count >29/nl and the complication of congestive heart failure. It is known that both older age (age > 60 years) and the complication of congestive heart failure are risk factors for venous thromboembolism (VTE). Platelet transfusion might not be suitable for patients with these two features, which would increase the risk of VTE and lead to a worse outcome. According to our findings, platelet transfusion may be harmful to patients with sepsis-induced thrombocytopenia. It seems that platelet transfusion is not an effective rescue therapy and does not improve the prognosis in patients with sepsis-induced thrombocytopenia.

There are still several limitations to the present study. First, as a retrospective design, the adjustment of missing relevant data was not allowed. Although we did perform propensity score matching to reduce the imbalance, the estimation of the propensity score could only be based on the acquirable data. Second, bacterial species and sources were not recorded in our data, and the purpose of platelet transfusion was also unknown. Thus, these two aspects could not be included in the analysis. Third, other outcomes (such as bleeding, thrombosis, and infection) were absent, and further hypotheses about the reasons for the observed association were not possible. Last, since this was an observational study, the association between platelet transfusion and clinical outcomes was not a causality. Therefore, well-organized prospective randomized clinical trials are required to verify the role of platelet transfusion in sepsis-induced thrombocytopenia.

In conclusion, platelet transfusion is associated with increased in-hospital mortality in septic patients with severe thrombocytopenia (a platelet count ≤ 50/nl). However, it may not be associated with 90-day mortality or the length of ICU stay. Further prospective studies will be needed in the future to confirm these results.

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A.Z. conceived the study and extracted the data. A.Z. and S.W. performed the statistical analyses. A.Z. and S.W. wrote the manuscript. J.P. and Q.C. reviewed the data analysis and interpretation and revised the manuscript for the final version. All authors read and approved the final manuscript. We thank Dr. Xianwei Zhang (The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China) and Dr. Jiejie Cai (The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang) for their help in this revision.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The datasets are available in the MIMIC III database (https://physionet.org/works/MIMICIIIClinicalDatabase/files/).

ORCID

Aiming Zhou https://orcid.org/0000-0002-7308-1951

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ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

Haematological patients' perception of home transfusions: Effect of the COVID-19 pandemic

Odit Gutwein[1] | Katrin Herzog Tzarfati[1] | Arie Apel[1] | Naomi Rahimi-Levene[1] | Hani Michaeli[1] | Liza Barki-Harrington[2] | Maya Koren-Michowitz[1,3]

[1]Department of Hematology, Shamir Medical Center (Assaf Harofeh), Zerifin, Israel

[2]Department of Human Biology, Faculty of Natural Sciences, University of Haifa, Haifa, Israel

[3]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Correspondence
Odit Gutwein, Department of Hematology, Shamir Medical Center (Assaf Harofeh), Zerifin, 70300, Israel.
Email: oditg@shamir.gov.il

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Abstract

Background and Objectives: The COVID-19 pandemic has led to a growing interest in hospital-at-home programmes, including home transfusion services. We studied whether the pandemic had influenced patients' perception of home transfusions.

Materials and Methods: We conducted a survey among haematology patients who receive transfusions in the hospital day care facility. Patients were asked about the burden of day care transfusions and whether they would prefer receiving home transfusions. The survey was conducted during the COVID-19 pandemic, and the results were compared with a survey performed before the pandemic (baseline).

Results: Sixty patients were included in the COVID-19 cohort and 31 patients in the baseline cohort. There was a non-significant decrease in the proportion of patients willing to receive home transfusions during the pandemic compared with baseline (35% vs. 47%, respectively, $p = 0.28$). More patients in the COVID-19 cohort were afraid to receive home transfusions (60% compared with 48% at baseline, $p = 0.29$), and fewer patients believed that hospital transfusion impaired their quality of life (19% compared with 36% at baseline, $p = 0.09$). These unexpected results may be partly attributed to the shorter time needed to arrive at the hospital during the pandemic and a greater fear of having transfusion-related adverse effects at home.

Conclusions: Our results show that the pandemic did not increase the willingness of patients to receive home transfusions, with a non-significant drift towards refusal of home transfusions. Patients' opinions should be taken into consideration when planning for future home transfusion services, by creating a comprehensive approach to patients' needs.

Keywords

COVID-19, home transfusion, hospital at home

Highlights

- A survey of haematological patients' perception of home transfusions was conducted during the COVID-19 pandemic and was compared with pre-pandemic results.
- Patients' willingness to receive home transfusions did not increase during the pandemic.
- These results should be taken into account when planning for future home transfusion services.

INTRODUCTION

The emergence of the COVID-19 pandemic has created an urgent need for re-organization of healthcare delivery methods. Overloaded hospitals with COVID-19 patients, together with the demand for social distancing, have shifted health services to the outpatient setting. Examples include a dramatic growth in the use of telemedicine [1], hospital-at-home units [2] and the implementation of technological solutions for remote patient monitoring [3].

As the haemato–oncology patient population is especially vulnerable to COVID-19 morbidity and mortality and cancer treatment interruptions, accelerated attempts to employ home care units for anti-neoplastic treatments and supportive care were implemented [4–7].

One of the unique characteristics of haemato-oncology patient care is the need for regular transfusions. Transfusion-dependent patients are characterized by high symptom burden and are often elderly, fragile with a short life expectancy. The current practice of blood product administration is almost exclusive to the hospital setting. Although home transfusion services are available in some countries, logistic and safety concerns limit their use [8]. The accelerated shift in healthcare delivery during the COVID-19 pandemic could potentially promote the development of home transfusion units worldwide. In Israel, transfusions are given only in the hospital setting, and according to a pre-pandemic survey evaluating the willingness of transfusion-dependent Israeli patients to receive home transfusions, more than half of the patients had a positive opinion on receiving home transfusions [9]. Given the severe impact of the COVID-19 pandemic on health services, we re-examined how the current pandemic influenced patients' perception of transfusions and the option to receive home transfusions.

MATERIALS AND METHODS

Patients

This is a single-centre study conducted at the Haematology Institute at Shamir Medical Center in Israel. An anonymous questionnaire was offered to all patients aged ≥18 years who receive regular blood product transfusions (red blood cells [RBC], platelets [PLT], or intravenous immunoglobulin transfusions [IVIG]) in the day care unit. Transfusion service was available only in the hospital setting. Data were collected at two time periods: at baseline (between October 2019 and February 2020) and during the COVID-19 pandemic (between April 2020 and October 2021). Surveys conducted during the pandemic took place in the initial four pandemic waves, with a total of 1,300,000 confirmed cases in Israel during that period. The Israeli vaccination programme started in December 2020, and by October 2021, 61% of the Israeli population had received two doses of COVID-19 vaccine (BNT162b2, Pfizer BioNTech vaccine) and 42% received the third (booster) dose [10]. Questionnaires given at baseline were previously reported as part of a multi-centre cross-sectional survey in Israel [9]. During the pandemic, questionnaires were only given at our centre, with the intention of comparing the two time periods. Only patients from Shamir Medical Center are included in this analysis. Although we tried to prevent it, there is a possibility that a few patients participated in both study cohorts, but due to the anonymous nature of the questionnaire, we do not have complete information. The study was approved by the local Institutional Review Board committee and informed consent was waived.

Study questionnaire

A sample of the questionnaire is available in Appendix S1. Questions included demographics, diagnoses, type and frequency of blood product transfusions and prior adverse reactions to transfusion, the effect of transfusions on quality of life (QOL), and whether home transfusion would improve QOL. The questionnaire was available in four prevalent languages in Israel (Hebrew, Arabic, Russian and Amharic).

Statistical analysis

Categorical variables are described as frequency and percentage. Age variable was evaluated for normal distribution using the Kolmogorov–Smirnov test and is reported as the median and interquartile range (IQR). Chi-square test and Fisher's exact test were used to compare categorical variables between groups, and Mann–Whitney test was applied to compare age. The multi-category variables were dichotomized into two categories for evaluation purposes (Appendix S1) and were compared using the same methods. All statistical tests were two-sided and $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS statistical software (IBM SPSS Statistics for Windows, version 25, IBM Corp., Armonk, NY, 2017).

RESULTS

Ninety-one patients who receive regular transfusions in the day care unit answered the questionnaire, 31 at baseline and 60 during the COVID-19 pandemic. At baseline, the average monthly day care visits were 322, and the average monthly number of visiting patients was 131. During the pandemic, the average monthly day care visits were 330, and the average monthly number of visiting patients was 138, essentially identical to the baseline rates. The majority of day care visits (95%) were of haemato-oncology patients and 5% of the visits were related to non-malignant haematology conditions.

Patients' characteristics are shown in Table 1. The mean age was 73 years, and 48% were male. Most patients answered the questionnaire in Hebrew. The reported diagnoses were myeloid (acute myeloid leukaemia, myelodysplastic syndrome and myelofibrosis) in 50% of patients and lymphoid (lymphoma, chronic lymphocytic leukaemia and multiple myeloma) in 23%. Twenty-seven percent of patients reported having anaemia or thrombocytopenia, with no specific diagnosis.

TABLE 1 Patient's characteristics

	Baseline cohort $N = 31$	COVID-19 cohort $N = 60$	Total $N = 91$	p $N = 31$
Age, years, median (range)	73 (24–95)	74 (47–96)	73 (24–96)	0.353
Gender *n* (% of evaluable)				
Male	12 (41%)	29 (52%)	41 (48%)	0.360
Female	17 (59%)	27 (48%)	44 (52%)	
Education *n* (% of evaluable)				
Academic	5 (17%)	17 (32%)	22 (26%)	0.130
Not academic	25 (83%)	37 (69%)	62 (74%)	
Language *n* (% of evaluable)				
Hebrew	27 (87%)	47 (78%)	74 (81%)	0.31
Other than Hebrew[a]	4 (13%)	13 (22%)	17 (19%)	
Diagnosis *n* (% of evaluable)				
Myeloid neoplasia	11 (37%)	33 (57%)	44 (50%)	0.18
Lymphoid neoplasia	8 (27%)	12 (20%)	20 (23%)	
Anaemia\thrombocytopenia	11 (37%)	13 (22%)	24 (27%)	

[a]Arabic = 1; Russian = 15; Amharic = 1.

Compared with the baseline cohort, the COVID-19 cohort had a higher proportion of male patients (52% compared with 41%), a higher number of patients with myeloid neoplasm (57% compared with 37%), a lower proportion of Hebrew-speaking patients (78% compared with 87%) and higher education (32% compared with 17%). These differences were not statistically different.

Patient's transfusion routine and experience

The most commonly reported transfusion product was RBC (91% of patients), followed by PLT (28% of patients) and IVIG (3%). Fifteen patients (20%) reported having a previous adverse reaction to transfusions, most commonly shivering ($n = 5$), and four patients reported having a previous serious adverse event. The frequency of transfusions was twice or higher per month in 52% of patients, while 48% required less frequent transfusions. The time travelled from home to the hospital was 1 h or more in 17% of patients, and the time spent in hospital was 4 h or more in 34%. Ninety-seven percent of patients were satisfied with the day care conditions. Twenty-five percent of patients believe that visiting the hospital for transfusion resulted in significant impairment of their QOL.

Compared with the baseline cohort, the COVID-19 cohort of patients had higher transfusion requirements (63% of patients requiring two or more transfusions per month compared with 52% in the baseline cohort) and a higher proportion of PLT transfusions (34% compared with 16%). A lower proportion of patients in the COVID-19 cohort reported having a significant impairment of QOL as a result of hospital transfusions (19% compared with 36%). These differences were not statistically significant. There was a trend towards a shorter time to get to the hospital during the pandemic: 12% of patients reported that it took 1 h or more compared with 27% at baseline ($p = 0.078$).

Patient's perceptions of home transfusions

Patients were asked if they believed home transfusions could improve their QOL, whether they were afraid of receiving home transfusions and whether they would select this option if available. As depicted in Figure 1, overall, 57% of patients believed that home transfusions could positively affect their QOL. Fifty-six percent of patients expressed fear related to getting transfusions at home. Concerns included losing connection with the hospital in 47% and fear of adverse effects in 41%. Only 39% of patients were willing to receive home transfusions if it were available. Compared with the baseline cohort, a higher proportion of patients in the COVID-19 cohort were afraid of home transfusions (60% compared with 48%, $p = 0.29$) and expressed fear of adverse events (45% compared with 32%, $p = 0.27$) although this was not statistically significant. A lower proportion of patients in the COVID-19 cohort were willing to receive home transfusions (35%) compared with the baseline cohort (47%) $p = 0.28$, but this was also not statistically significant.

We next examined potential associations between patients' characteristics and willingness to receive home transfusions (Table 2). Using the Hebrew questionnaire was more prevalent among patients who agreed to receive home transfusions at baseline, but not during the pandemic. Academic education and prolonged stay in the hospital tended to be more common in patients who agreed to receive home transfusions. This trend was observed in the COVID-19 cohort but not at baseline. Patients who believed that home transfusions could improve their QOL and patients who were not afraid of home

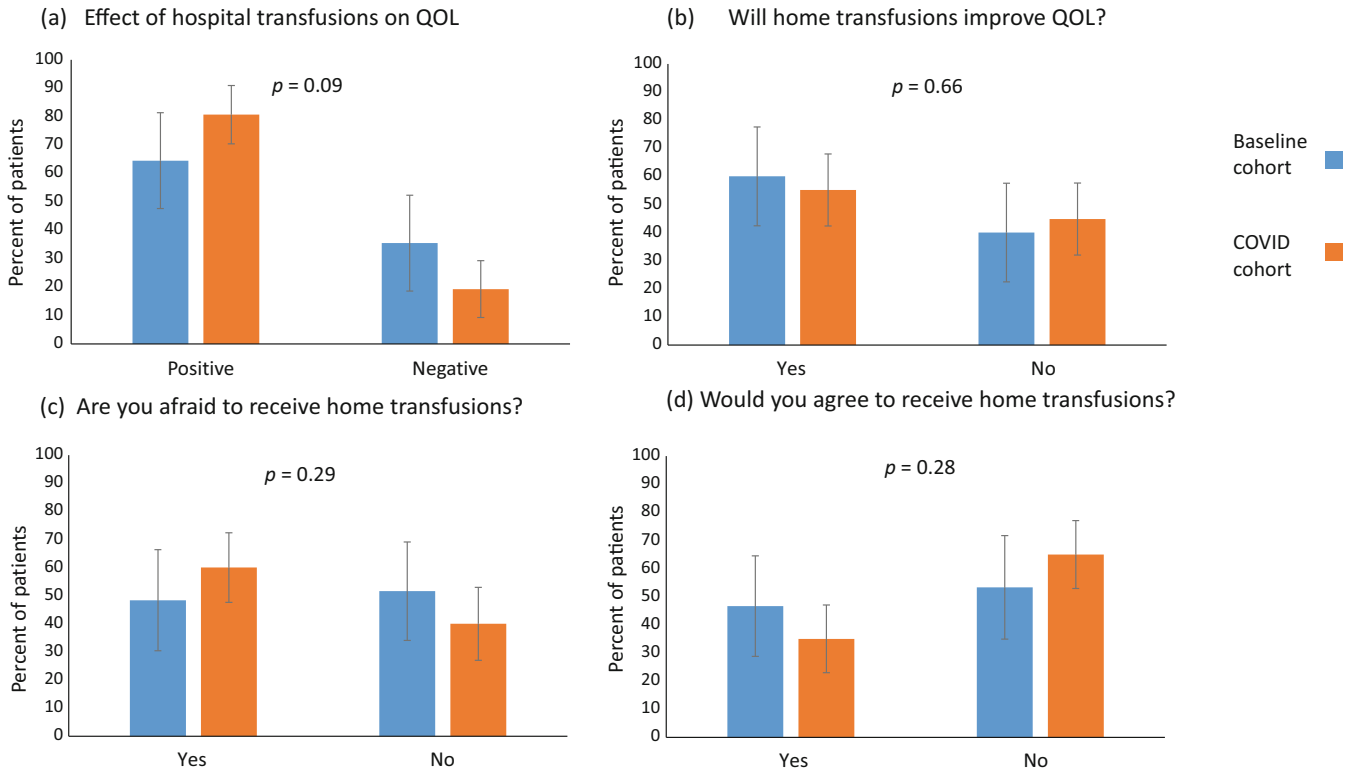

FIGURE 1 Patients' perception of hospital transfusion and transfusion at home. (a) Patients' response to whether in-hospital transfusions impaired their quality of life (QOL). (b) Patients' response to whether home transfusions will improve their QOL. (c) Patients response to whether they are afraid of home transfusions. (d) Patients' response to whether they would agree to home transfusions. Error bars represent 95% confidence intervals.

transfusions were significantly more likely to accept home transfusions in both time periods.

DISCUSSION

The shift in healthcare delivery during the COVID-19 pandemic has created opportunities for expanding and improving hospital-at-home services, including home transfusions. Decisions regarding healthcare policies should take into account technological and regulatory considerations as well as patients' perspectives and needs. Here we report the results of a survey among haematology patients regarding home transfusions. The results of the survey given during the COVID-19 pandemic were compared with pre-pandemic (baseline) results, aiming to capture trends in an era of health crisis and rapid healthcare reforms.

We found that the pandemic did not encourage patients to embrace the option of home transfusions. Only 35% of the COVID-19 cohort were willing to receive home transfusions, compared with 47% in the baseline cohort. During the pandemic, patients' opinions were mostly 'pro hospital', with less patients feeling that hospital transfusions impaired their QOL and more patients expressing fear of receiving home transfusions. These results were somewhat unexpected, especially when considering reports on the significant anxiety expressed by cancer patients during the pandemic from acquiring COVID-19, which could result in treatment interruptions [11–13], as well as patients' satisfaction with new healthcare modalities such as telehealth and hospitals at home [14–16].

The baseline (pre-pandemic) cohort of our study was part of a multi-centre Israeli survey of 385 patients, in which 52% of patients expressed willingness to receive transfusions at home [9]. The results of the multi-centre study showed that willingness to receive home transfusions was associated with the language chosen to fill in the questionnaire (Hebrew vs. Other), a parameter that represents ethnicity. Other factors associated with willingness to receive home transfusions included younger age, apprehension towards home transfusions, fear of adverse effects and a perception of negative effect of hospital transfusions on QOL.

When looking at 'pre-pandemic' data, our baseline cohort showed similar rate of agreement with home transfusions compared with the multi-centre study (47% and 52%, respectively). However, there were few differences between our local baseline cohort and the total population in the multi-centre study. The patients who participated in our baseline cohort were older than the multi-centre study population (median age 71 years compared with 66 years), with less academic education (17% compared with 40%) and more patients used local language (Hebrew) to answer the questionnaire (87% compared with 68%). There was no difference in those characteristics between our baseline and COVID-19 cohorts. In addition,

TABLE 2 Patients' characteristics and agreement to home transfusions

Willingness to receive home transfusions	Baseline cohort			COVID-19 cohort			All patients		
	Yes $N = 14$	No $N = 16$	p	Yes $N = 21$	No $N = 39$	p	Yes $N = 35$	No $N = 55$	p
Age, years, median (IQR)	70(66-75)	74(70-80)	0.472	76(67-82)	73(70-79)	0.561	74(66-81)	73(70-79)	0.857
Gender *n* (% of evaluable)									
Male	6 (46%)	6 (40%)	0.74	11 (58%)	18 (47%)	0.512	17 (53%)	24 (46%)	0.535
Female	7 (54%)	9 (60%)		8 (42%)	19 (53%)		15 (47%)	28 (54%)	
Education *n* (% of evaluable)									
Academic	2 (15%)	3 (19%)	>0.99	9 (47%)	8 (23%)	0.064	11 (34%)	11 (22%)	0.198
Not academic	11 (85%)	13 (81%)		10 (53%)	27 (77%)		21 (66%)	40 (78%)	
Language *n* (% of evaluable)									
Hebrew	14 (100%)	12 (75%)	0.102	17 (81%)	30 (77%)	0.989	31 (89%)	42 (76%)	0.149
Other	0	4 (25%)		4 (19%)	9 (23%)		4 (11%)	13 (24%)	
Prior adverse reaction to transfusion *n* (% of evaluable)	3 (21%)	2 (16%)	0.865	5 (24%)	8 (20%)	0.802	8 (23%)	10 (18%)	0.588
Frequency of transfusions *n* (% of evaluable) ≥2 per month	7 (50%)	7 (50%)	>0.99	13 (72%)	22 (58%)	0.302	20 (62%)	29 (56%)	0.543
Time spent to get to hospital *n* (% of evaluable) >1 h	4 (29%)	4 (27%)	>0.99	3 (14%)	4 (10%)	0.642	7 (20%)	8 (15%)	0.549
Length of hospital stay *n* (% of evaluable) >4 h	6 (46%)	4 (29%)	0.585	9 (45%)	11 (28%)	0.197	15 (46%)	15 (28%)	0.105
Satisfaction with hospital conditions *n* (% of evaluable)									
Satisfied	12 (86%)	16 (100%)	0.418	21 (100%)	38 (97%)	>0.99	33 (98%)	54 (94%)	0.558
Not satisfied	2 (14%)	0		0	1 (3%)		2 (6%)	1 (2%)	
Effect of hospital transfusions on QOL *n* (% of evaluable)									
Impair QOL	6 (43%)	4 (25%)	0.517	8 (40%)	3 (8%)	0.009	14 (44%)	7 (13%)	0.001
Not impair QOL	8 (57%)	12 (75%)		12 (60%)	36 (92%)		18 (56%)	48 (87%)	
Believe that home transfusions will improve QOL *n* (% of evaluable)									
Yes	11 (85%)	6 (38%)	0.01	20 (95%)	13 (34%)	<0.001	30 (91%)	19 (35%)	<0.001
No	2 (15%)	10 (62%)		1 (5%)	25 (66%)		3 (9%)	48 (87%)	
Fear from receiving home transfusions *n* (% of evaluable)									
No	4 (29%)	11 (69%)	0.028	7 (33%)	29 (74%)	0.004	24 (69%)	14 (27%)	<0.001
Yes	10 (71%)	5 (31%)		14 (67%)	10 (64%)		11 (31%)	40 (73%)	

Abbreviations: IQR, interquartile range; QOL, quality of life.

similar to the multi-centre trial, a trend towards an association between the language used and acceptance of home transfusions was demonstrated in the baseline cohort. However, the language used by patients did not seem to impact patients' preferences in the COVID-19 cohort, suggesting a more robust effect of the pandemic in all ethnic groups.

The impact of routine transfusions on QOL may be influenced by the time and effort related to the hospital visits. Indeed, in the multi-centre study, variables associated with the perception that hospital visits harm QOL [9] included frequency of hospital visits, time needed to reach the hospital, time spent in hospital and the in-hospital conditions. Interestingly, we found that a lower proportion of patients in the COVID-19 cohort reported QOL impairment compared with the baseline cohort (19% compared with 36%), and the only different potential contributor to QOL was a trend for shorter time required to arrive at the hospital in the COVID-19 cohort compared with the baseline one, which could be attributed to a decline in traffic volume.

A recent interview study of Australian haemato-oncology patients conducted during the COVID-19 pandemic has defined several aspects of patients' needs during the pandemic. Along with the fear of contracting COVID-19, patients emphasized a reduced sense of social connections and external support, feelings of loneliness, and difficulties in communicating with healthcare systems and providers [17]. Other studies have shown that half of the cancer patients were affected by loneliness during the pandemic [18, 19]. Such feelings could also explain why patients in our study preferred the familiar

setting of the day care facility rather than home transfusions. When asked about reasons for apprehension to home transfusions, a higher proportion of patients in the COVID-19 cohort were concerned about having side effects, although the percentage of patients who reported previous side effects was similar in the baseline and COVID-19 cohorts. The increased concern of safety issues when considering home treatment could be attributed to a greater awareness of side effects in light of the public discussion on COVID-19 vaccination, but it also suggests that the hospital setting is perceived as safe and protective despite the risk of contracting COVID-19.

Regular transfusions are an essential part of supportive care for haematology patients. Home transfusions have been used for decades, but this service is not widely available for most patients, including in Israel, where transfusions are given exclusively within the hospital setting. Recent publications evaluating home transfusions show that this procedure is feasible and associated with low rates of side effects [20, 21]. The COVID-19 pandemic has created a growing interest in administrating transfusions out of the hospital, motivating haematologists to change their transfusion practice and develop home transfusion services [22, 23]. Nevertheless, our data show that this may not necessarily reflect the preferences and wishes of many patients and that the demographics, social and psychological needs of haematology patients should be taken into account when planning future reforms, along with patients' education and reassuring programmes. A significant aspect of home transfusion services' success could be by addressing the need for a stable and trustful relationship with medical staff.

Our study has several limitations. This is a single-centre study, and the relatively small sample size limited our ability to detect statistically significant differences between the study cohorts. The questionnaire was created before the pandemic and did not include specific questions on factors that could be relevant in this era, including social distending considerations, vaccination history, the effect of isolation, treatment adherence and attitude towards new technologies. In addition, different phases of the pandemic could influence patients' opinions, but we do not have the data about the exact timing of survey filling for each patient. Although we tried to prevent it, a few patients might have participated in both study cohorts, but due to the anonymous nature of the questionnaire, we do not have detailed information.

In summary, in a survey of haematology patients, the COVID-19 pandemic did not increase the willingness of patients to receive transfusions at home. Patients express more 'pro-hospital' preferences and fear of being treated at home, although not reaching statistical significance. This perhaps reflects a fear of losing social and professional support, which could be greater than the fear of being infected by COVID-19. Learning about patients' perceptions is essential for the development of hospital-at-home programmes and should include a comprehensive approach to patients' needs.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

ORCID

Odit Gutwein https://orcid.org/0000-0003-0204-099X
Naomi Rahimi-Levene https://orcid.org/0000-0003-3411-886X
Maya Koren-Michowitz https://orcid.org/0000-0002-7223-328X

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

Early and out-of-hospital use of COVID-19 convalescent plasma: An international assessment of utilization and feasibility

Arwa Z. Al-Riyami[1] | Lise Estcourt[2] | Naomi Rahimi-Levene[3] | Evan M. Bloch[4] | Ruchika Goel[4,5] | Pierre Tiberghien[6] | Jean-Baptiste Thibert[6] | Mie Topholm Bruun[7] | Dana V. Devine[8,9] | Richard R. Gammon[10] | Silvano Wendel[11] | Michel Toungouz Nevessignsky[12] | Rada M. Grubovic Rastvorceva[13,14] | Adaeze Oreh[15] | Iñigo Romon[16] | Karin van den Berg[17,18,19] | Junichi Kitazawa[20] | Gopal Patidar[21] | Cynthia So-Osman[22,23] | Erica M. Wood[24] | on behalf of the ISBT COVID-19 Convalescent Plasma Working Group

[1]Department of Hematology, Sultan Qaboos University Hospital, Muscat, Oman

[2]NHS Blood and Transplant & Radcliffe Department of Medicine, University of Oxford, Oxford, UK

[3]Blood Bank, Shamir Medical Centre, Assaf Harofeh MC, Zerifin, Israel

[4]Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

[5]ImpactLife Blood Centre and Department of Internal Medicine, Southern Illinois University School of Medicine, Springfield, Illinois, USA

[6]Etablissement Français du Sang, Rennes, France

[7]Department of Clinical Immunology, Odense University Hospital, Odense, Denmark

[8]Centre for Innovation, Canadian Blood Services, Vancouver, Canada

[9]Centre for Blood Research, University of British Columbia, Vancouver, Canada

[10]Scientific Medical and Technical Direction, OneBlood, Orlando, Florida, USA

[11]Blood Bank, Hospital Sírio-Libanês Blood Bank, São Paulo, Brazil

[12]Belgian Red Cross, Suarlée, Namur, Belgium

[13]Institute for Transfusion Medicine of RNM, Skopje, North Macedonia

[14]Faculty of Medical Sciences, University Goce Delcev, Štip, North Macedonia

[15]National Blood Service Commission, Federal Ministry of Health, Abuja, Nigeria

[16]Hematology Department, University Hospital Marques de Valdecilla, Santander, Spain

[17]Transfusion Medicine and Technical Services Division, South African National Blood Service, Johannesburg, South Africa

[18]Department of Medicine, University of Cape Town, Cape Town, South Africa

[19]Division of Clinical Haematology, University of the Free State, Bloemfontein, South Africa

[20]Department of Genomic Medicine, Aomori Prefectural Central Hospital, Aomori, Japan

[21]Department of Transfusion Medicine, All India Institute of Medical Sciences, New Delhi, India

[22]Unit Transfusion Medicine, Sanquin Blood Bank, Amsterdam, the Netherlands

[23]Department of Haematology, Erasmus Medical Centre, Rotterdam, the Netherlands

[24]Transfusion Research Unit, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia

Correspondence
Arwa Z. Al-Riyami, Department of Hematology, Sultan Qaboos University Hospital, P.O. Box 38, Postal code 130, Muscat, Oman.
Email: arwa@squ.edu.om

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Abstract

Background and Objectives: The use of coronavirus disease 2019 (COVID-19) convalescent plasma (CCP) in the treatment of patients with severe acute respiratory syndrome-2 infection has been controversial. Early administration of CCP before hospital admission offers a potential advantage. This manuscript summarizes current trials of early use of CCP and explores the feasibility of this approach in different countries.

Materials and Methods: A questionnaire was distributed to the International Society of Blood Transfusion (ISBT) CCP working group. We recorded respondents' input on existing trials on early/outpatient CCP and out-of-hospital (OOH)/home transfusion (HT) practices in their countries and feedback on challenges in initiating home CCP infusion programmes. In addition, details of existing trials registered on *clinicaltrials.gov* were summarized.

Results: A total of 31 country representatives participated. Early/OOH CCP transfusion studies were reported in the United States, the Netherlands, Spain and Brazil. There were a total of six published and five ongoing trials on the prophylactic and therapeutic early use of CCP. HT was practised in Australia, the UK, Belgium, France, Japan, Nigeria, the Netherlands, Spain, Italy, Norway, the United States and some provinces in Canada. Thirty-four representatives indicated a lack of OOH CCP or HT in their institutions and countries. Barriers to implementation of OOH/HT included existing legislation, lack of policies pertaining to outpatient transfusion, and associated logistical challenges, including lack of staffing and resources.

Conclusion: Early administration of CCP remains a potential option in COVID-19 management in countries with existing OOH/HT programmes. Legislation and regulatory bodies should consider OOH/HT practice for transfusion in future pandemics.

Keywords

convalescent plasma, COVID-19, home transfusion

Highlights

- Data on the benefit of early administration of COVID-19 convalescent plasma (CCP) are emerging.
- Out-of-hospital CCP administration is associated with different logistic challenges that need to be taken into account by institutions/facilities that are considering the implementation of this practice.

INTRODUCTION

Transfusion of convalescent plasma from recovered individuals has been tried as a therapeutic approach in multiple epidemics and pandemics of novel pathogens [1]. In the context of the coronavirus disease 2019 (COVID-19) pandemic, while vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were awaiting development, testing and deployment, COVID-19 convalescent plasma (CCP), hyperimmune globulins, and antiviral monoclonal antibodies each offered an attractive and feasible option for passive immunization.

COVID-19 convalescent plasma offers a readily available therapy to provide neutralizing antibodies for COVID-19-infected patients and via other mechanisms – for example, via modifying inflammatory markers [2]. Multiple clinical trials have studied the effectiveness of CCP administration in unselected hospitalized patients with moderate to severe COVID-19; overall, these trials have not demonstrated a benefit of CCP on all-cause mortality, progression of the disease or hospital stay [3–5]. The published trials have shown contradictory findings, likely in part due to heterogeneity in regard to the timing, dose or content of CCP administered, or severity of the infection

[4–6]. No benefit has been demonstrated in unselected subgroups of hospitalized patients; however, some studies do indeed suggest efficacy in subgroups who have surrogate characteristics for the probable lack of endogenous neutralizing antibodies. CCP is most likely to be effective if administered early in the disease, before the patient's own antibody response, in particular, in patients who cannot mount their own immune response, such as the immunocompromised or immune deficient patients [7, 8]. Early administration is also believed to prevent innate immune cell migration and avoid lung damage [9]. CPP effectiveness could also be influenced by anti-SARS-CoV-2 antibody titres in the recipients before administration [2].

Research to evaluate the efficacy of early CCP administration introduces several challenges. These include setting up the clinical trials, identifying and referring patients early in the disease, managing the logistics of CCP transfusion and patients' follow-up, including managing any adverse events. Home transfusion (HT) and out-of-hospital (OOH) are attractive options for early CCP administration and have been practised for standard blood components. However, OOH/HT requires special attention to manage the logistics, complexities and risks of being distant from hospital care. The availability of OOH/HT in different countries and/or the feasibility of establishing an outpatient transfusion programme that could support early CCP administration is unknown.

The International Society of Blood Transfusion (ISBT) initiated a multidisciplinary group to review existing practices on CCP use. A subgroup was formed to review existing practices and trials in early/outpatient CCP use and to assess its potential application via OOH/HT in different countries. This manuscript aims to summarize the current status of early/outpatient CCP use and existing OOH/HT practices.

METHODS

A questionnaire was developed to examine early and outpatient CCP transfusion (Appendix S1). Data were collected from 1 May to 30 September 2021. Participation was voluntary, and consent was obtained by filling in the questionnaire. The questionnaire included two sections; one for participants who have early/outpatient CCP trials in their institutions or countries, and one for participants who do not have such programmes. The first section included 14 questions covering indications for use, patient inclusion and exclusion criteria, timing of CCP administration, follow-up, trial primary and secondary outcomes, product characteristics, administration logistics and funding sources. The second section included details on CCP use during the COVID-19 pandemic and perceived challenges associated with establishing an early/outpatient CCP programme. In addition, six questions addressed the existing practices of OOH/HT transfusion of standard blood components, how transfusion of quarantined individuals due to COVID-19 is facilitated, where transfusions are administered, and what additional precautions are followed. All survey participants were invited to answer questions on existing OOH/HT transfusion programmes in their countries (if present), how they are facilitated, and how patients are monitored for adverse events.

The questionnaire was distributed to members of the ISBT CCP working group and the European Blood Alliance. We also obtained information from the ISBT Board of Directors on practices in countries that were not represented in the working group. Responses received were summarized, and descriptive analysis was performed.

Trials registered on clinicaltrials.gov up to 14 February 2022, were searched by a research team member. The search strategy to identify completed and ongoing studies were performed using the World Health Organization (WHO) COVID-19 Global literature on coronavirus disease Research Database, MEDLINE, Embase, the Cochrane COVID-19 Study Register and the Epistemonikos COVID-19 L*OVE Platform. Data on pre-hospital/early use of CCP were summarized.

RESULTS

A total of 44 country representatives from 32 countries were invited to participate. Forty participants from 31 countries provided information on the existence of early/outpatient CCP and/or OOH/HT transfusion programmes (response rate; 90.9%) (Figure 1). Nineteen participants, representing 17 countries, shared a description of CCP OOH/HT and outpatient transfusion programmes for COVID-19 patients in their institutions (Table S1). This included national blood establishments/blood centres ($n = 6$), regional blood services/blood centres ($n = 2$) and hospital-based transfusion services and blood banks ($n = 11$). Other participants confirmed the lack of OOH/HT transfusion programmes in their institutions and countries.

Early/outpatient CCP use

Early/outpatient CCP trials were conducted in the United States, the Netherlands and Spain. Details of these are described below. In addition, at the time of the write-up, a multicentre trial (Germany, France, the UK) was starting.

A centre in Brazil has a compassionate use programme with the administration of locally collected pathogen-reduced CCP (Intercept, Cerus, USA) with a minimum neutralizing antibody titre of 1:160 for patients >60 years with co-morbidities. CCP (200 ml) is transfused within 5 days of symptom onset, and a positive test for SARS-CoV-2. CCP is administered in an outpatient setting (day-care, emergency room, COVID ward). The primary outcome is death within 28 days, while the secondary outcome is the need for hospitalization. Patients are followed up in person by physicians, and samples are collected for neutralizing antibody testing. The cost of CCP is covered by the patient or his/her health insurance.

Home transfusion

Home transfusion is practised in Australia, the UK, Belgium, France, Japan, Nigeria, the Netherlands, Spain, Italy, Norway, the United States and some provinces in Canada (Figure 1, Table S2). In the UK, HT was

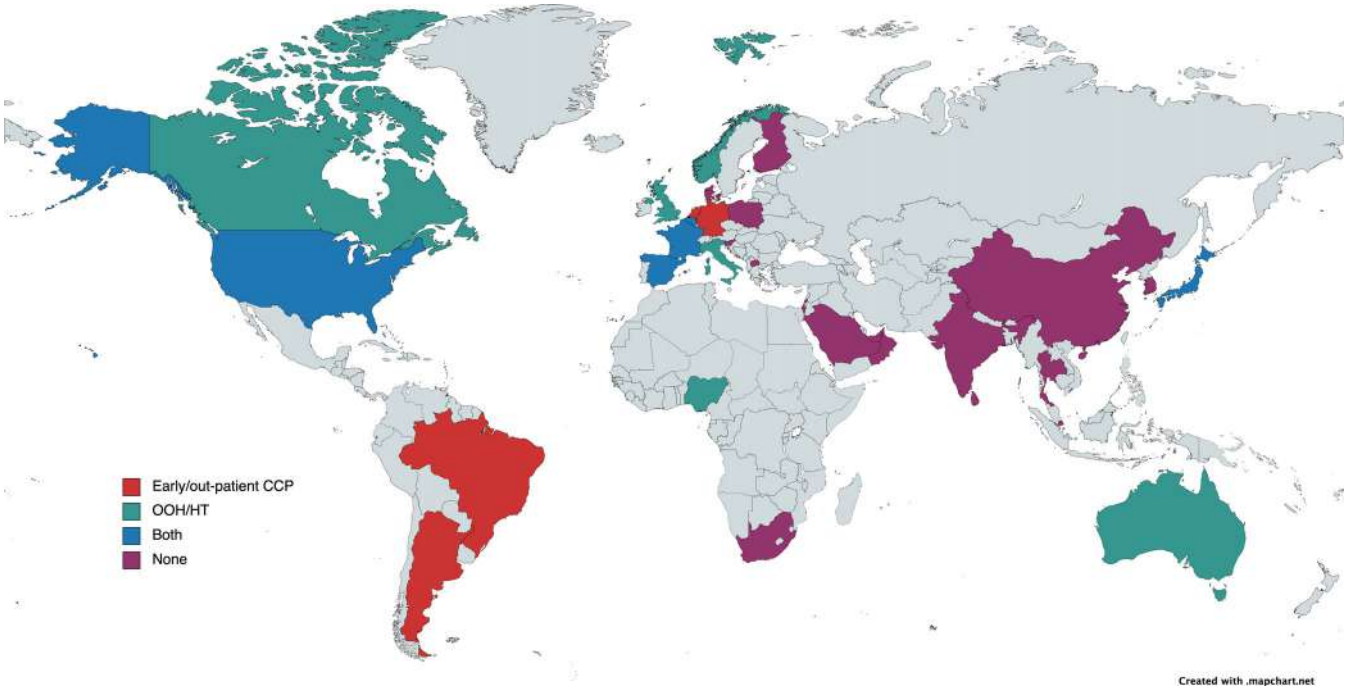

FIGURE 1 Geographic distribution of survey respondents and other participants ($n = 38$)

implemented before the COVID-19 pandemic, but its use has increased substantially during the pandemic. HT is managed by individual hospitals. In France, HT has long been authorized in accordance with existing guidelines. Transfusions are mainly for red blood cells, less commonly for platelets and rarely for plasma. The transfusion is carried out by trained physicians or by medical midwives or nurses, provided that a valid transfusion request is present, and a physician is available to intervene at any time. The practitioner, however, has to be authorized for transfusion in a home-care setting. In Spain, HTs are possible if occurring within 30 min drive from a healthcare facility with ambulance services. Transfusion is performed by a nurse. In Nigeria, several hospitals have home-based care programmes, including HTs that take place under supervision by the clinical team.

The practice of monitoring patients varied between the different countries. In the UK, a nurse needs to be present during the transfusion and for 30 min post-transfusion. Patients are given contact details to report if feeling unwell post-transfusion. A similar practice is followed in Japan. In Spain, the nurse needs to be present for the first 15 min. In France, transfusion is monitored at least for the first 15 min and at regular intervals thereafter, and the healthcare provider must be available for at least 2 h after the end of the transfusion. Family members are instructed to monitor the patient for the first 2 h post-transfusion.

Transfusion of patients with COVID-19

For outpatients with COVID-19 infection, there was variation in the practice of where transfusion of standard blood products was undertaken should require while being in quarantine outside the hospital (Table S2). This included the emergency room ($n = 9$), COVID wards ($n = 8$), and home ($n = 7$). In a regional blood service/blood centre in the United States, a dedicated outpatient infusion tent is used for this purpose. In Australia and the UK, the transfusion practice varies. In Denmark, Israel, North Macedonia and South Korea, patients are admitted if they require a blood transfusion, while in Belgium, this is arranged through the patient's general practitioner. Standard COVID-19 precautions while transfusing patients were reported to be followed by all participants.

Challenges for establishing an OOH/HT CCP programme

Institutions described different challenges with an OOH/HT CCP programme. These included obtaining institutional review board approval to set up a clinical trial and patient enrolment within a narrow window from symptom onset/diagnosis. Other challenges included the logistics of transfusing CCP outside of a hospital setting and controlling the flow of patients with COVID-19 separately from uninfected patients if transfused in the day-care or emergency room.

Perceived obstacles to starting an OOH/HT CCP programme in countries included the existing regulations/legislation and/or lack of policies pertaining to transfusion outside hospital premises and infrastructure to accommodate a change in practice. Other obstacles included the need for resources (e.g., staffing, funding, equipment for maintaining the cold chain during transfer) and managing the associated logistics. In Thailand, CCP, prepared by the National Blood Centre in Bangkok, is restricted 'for inpatient cases only'.

TABLE 1 Completed studies of COVID-19 convalescent plasma in early/outpatient setting

Study	Country/ies	Intervention(s)	Number analysed	Patient population	Primary outcome(s)	Neutralizing antibody titre	Viral variants considered in analyses
Prophylaxis							
Shoham et al., 2022 (CSSC-001) [13][a] NCT04323800	USA	200–250 ml CCP 200-250 ml non-immune plasma[d]	180 (Planned 500)	Age ≥18 Close contact exposure to person with COVID-19 within 96 h of randomization (and 120 h of receipt of plasma) *Exclusions*:[c] • Previous COVID-19 • COVID-19 symptoms • Laboratory evidence of COVID-19 at time of screening • Receipt of any blood product ≤120 D	Cumulative incidence of development of SARS-CoV-2 infection (symptoms compatible with infection and/or + molecular testing) [D28] Cumulative incidence of serious adverse events [D28] Cumulative incidence of grade 3 and 4 adverse events [D28]	≥ 1:320	No Recruited June 2020 to March 2021
Therapeutic (asymptomatic)							
No completed studies							
Therapeutic (mild disease)							
Libster et al., 2021 [6] NCT04479163	Argentina	250 ml CCP 250 ml saline (placebo)	160	Age ≥75 or 65 to 74 and co-morbidity Confirmed SARS-CoV-2 mild illness, not requiring hospitalization ≤72 h from symptom onset	Development of severe disease – defined as RR ≥30 breaths/min or oxygen saturations <93% on air, or both	>1:1000 anti–S IgG SARS-CoV-2	No Recruited June–October 2020
Sullivan et al., 2022 (CSSC-004)[a] [12] NCT04373460	USA	~250 ml CCP ~250 ml non-immune plasma[d]	1181 (Planned 1344 participants)	Age ≥18 (stratified < vs. ≥65 years) Confirmed SARS-CoV-2 not requiring hospitalization ≤8 D from symptom onset *Exclusions*:[c] • Hospitalized or expected to be hospitalized within 24 h of enrolment • Receiving any treatment drug for COVID-19 within previous 14 D • Inability to adhere to protocol • Receipt of monoclonal anti-bodies • Psychiatric or cognitive illness or recreational drug/alcohol use	Cumulative incidence of hospitalization or death before hospitalization [D28] Cumulative incidence of treatment-related serious adverse events [D28] Cumulative incidence of treatment-related grade 3 or higher adverse events [D90]	≥ 1:320	No Recruited June 2020–October 2021 90% of CCP was donated between April and December 2020
Bart Rijnders et al., 2020 (CoV-Early)[a] [14, 15] NCT04589949	Netherlands	300 ml CCP 300 ml non-immune plasma[d]	420 (Planned 690)	Age ≥70 OR 50–69 AND ≥1 risk factors[b] OR 18–49 and severely immunocompromised RT-PCR-confirmed COVID-19 ≤7 D from symptom onset	Highest disease status [D28]	1/160 Sanquin method, or 1/320 Viroscience method	Recruited November 2020–July 2021 for first analysis

(Continues)

TABLE 1 (Continued)

Study	Country/ies	Intervention(s)	Number analysed	Patient population	Primary outcome(s)	Neutralizing antibody titre	Viral variants considered in analyses
				Exclusions:[c] • Life expectancy <28D • Known IgA deficiency or TRALI • Admission to hospital			
Alemany et al., 2022 (ConV-ert) [11, 15] NCT04621123	Spain	200–300 ml methylene blue-treated CCP 200–300 ml saline (placebo)	376 (Enrolled 384)	Age ≥50 Confirmed SARS-CoV-2 by PCR or antigen rapid test ≤5 D Symptom onset (mild or moderate) ≤7 D *Exclusions*:[c] • Pregnant, breastfeeding • Severe or critical COVID-19 • Current hospital admission • History of previous confirmed SARS-CoV-2 infection. • Previous COVID-19 vaccination • Significant liver dysfunction • Chronic kidney disease ≥stage 4, or need of dialysis • Increased risk of thrombosis • Known IgA deficiency with anti-IgA antibodies • Disease in which 200-300 ml fluid volume a risk • Inability to adhere to protocol	Hospitalization rate [D28] SARS-CoV-2 viral load [D7]	EUROIMMUN ratio ≥6	Recruited November 2020 to July 2021 for first analysis
Emergency Room							
Korley et al., 2021 (C3PO) [10] NCT04355767	USA	250 ml CCP 250 ml saline (placebo)	511	Age ≥50 or ≥18 and co-morbidity Confirmed SARS-CoV-2 not requiring hospitalization ≤7 D from symptom onset	Disease progression after randomization [D15] (composite of hospital admission for any reason, emergency or urgent care, or death without hospitalization)	Median neutralizing antibodies 1:640 (IQR 468 to 1702)	No Recruited August 2020–February 2021

Abbreviations: CCP, COVID-19 convalescent plasma; D, days; IQR, interquartile range; RR; respiratory rate; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TRALI, Transfusion Related Acute Lung Injury.

[a]Additional information provided in survey.

[b]Obesity, male gender, cardiac, renal, rheumatic or pulmonary disease, and immunodeficiency.

[c]History of prior reactions to blood transfusion.

[d]Plasma collected in 2019, or obtained from persons who tested seronegative for SARS-CoV-2 after Dec. 2019.

Respondents from Bhutan, Nigeria and Japan indicated that there were no CCP programmes in their respective countries.

Another major challenge is the lack of policies and procedures for monitoring and managing adverse reactions post-transfusion in an OOH/home setting. This included defining responsibilities and duration of monitoring patients after transfusion for adverse reactions, and managing these if they occurred, especially if severe. Some indicated the lack of willingness and confidence of the healthcare providers and the caregivers in handling the transfusion.

Published trials

There were six completed randomized control trials on the use of CCP in an outpatient setting or emergency room setting [6, 10–14] (Table 1). Three of the peer-reviewed trials enrolled patients with confirmed SARS-CoV-2 infection to one unit of high-titre CCP versus placebo [6, 10, 11]. Libster et al. [6], treated older patients, mean age 77.2 ± 8.6 years old, very early after symptom onset (within 72 h) who did not need emergency or hospital care. This trial showed the benefit of early administration of high titre CCP in mildly ill, infected older adults with reduced progression to severe disease. Korley et al. (C3PO) [10] and Alemany et al. (ConV-ert) [11] treated younger patients (median 54 and 56 years respectively) within 7 days of symptom onset. Korley et al. sought to determine whether an infusion of high-titre CCP would prevent progression to severe COVID-19 if given to patients at high risk of severe COVID-19 who present to the emergency room (composite of hospital admission for any reason, seeking emergency or urgent care, or death without hospitalization). The ConV-ert study compared standard medical treatment plus methylene-blue treated CCP versus normal saline. No benefit was seen in the primary or secondary outcomes for either trial. In the Korley et al. trial, more participants were admitted to the hospital directly from the emergency department in the CCP arm than in the placebo arm (19 vs. 6). In a post hoc sensitivity analysis that excluded patients admitted to the hospital during their index visit, the posterior probability of superiority of CCP was 93% in the intention-to-treat population. The Convalescent Plasma to Limit SARS-CoV-2 Associated Complications (CSSC-004) trial [12] randomized adult outpatients with COVID-19 within 9 days of symptom onset to receive high-tier CCP versus non-immune plasma, thus demonstrating significantly fewer cases of hospitalization (i.e., the primary endpoint) in those who received CCP as compared to controls (relative risk reduction, 54%). The CSSC-001 [13] compared high-titre CCP versus non-immune plasma as post-exposure prophylaxis. Participants with close contact exposure to someone with confirmed COVID-19 were enrolled; all were negative for SARS-CoV-2 at the time of enrolment. CCP was administered within 120 h of exposure, and patients with symptomatic or asymptomatic COVID-19 infection at the time of screening were excluded. The primary outcome was SARS-CoV-2 infection. The trial was stopped early due to the increased use of vaccination. There was no significant difference seen between the two arms in the number of participants who developed SARS-CoV-2 infection ascertained by positive reverse transcription polymerase chain reaction (RT-PCR) testing by study day 28. The CoV-Early [14] is a therapeutic trial that enrolled patients aged 50 years or older within a week of symptom onset to receive CCP versus non-immune plasma. CoV-Early was analysed together with ConV-ert on a total of 797 patients within the first 7 days of symptoms using a Bayesian analysis [15]. The results showed no impact on the rate of hospitalization or mortality.

In CSSC-001 and CSSC-004, CCP transfusion was performed in a research unit at hospital sites, and follow-up was undertaken in a specific tent adjacent to the hospital. In the CoV-Early trial, patients were followed up at least by phone to evaluate their disease status and severity on a 5-point scale. Laboratory testing was performed by attendance at the day-care unit/hospital for a subgroup of patients.

Ongoing trials

There are five ongoing/planned trials on early/outpatient and OOH CCP use [16–20]. These trials varied in their source of funding from the government (three; one- USA, one- Germany, one- international); healthcare companies (one; USA); or unclear funding sources (one; Spain) (Table S3). All are therapeutic trials; four use standard-of-care as the comparator, and the fifth (Spain) uses standard plasma. In these therapeutic trials, the time of CCP administration from symptom onset varies and ranges from <96 h to ≤14 days. None of the trials included children.

The German trial is a multicentre four-arm trial that compares CCP, camostat mesylate, standard of care, and a placebo to camostat mesylate in a 2:2:1:1 ratio, in symptomatic high-risk patients with confirmed SARS-CoV-2 infection within 3 days of symptom onset and diagnosis [16]. The two ongoing trials from the United States compared CCP with the standard of care, one within 96 h of symptom onset in patients with confirmed SARS-CoV-2 infection plus one high-risk feature, allowing cross-over to the CCP arm should the patient require hospitalization for progression of COVID-19 disease [17]. The other trial enrols symptomatic patients with mild/moderate laboratory-confirmed disease <14 days from symptom onset [18].

The international trial, which is starting in Germany at the time of writing, aims to assess the effectiveness of CCP (very-high titre plasma [neutralizing Ab titre ≥1:640 against delta variant]) in two different cohorts, (1) older patients (≥ 70 years) or patients with co-morbidities, (2) patients with immunosuppression [19]. The Spanish trial stopped recruitment early due to lack of efficacy of CCP in preventing progression to a severe form of COVID-19 [20]. No trial data are available at the time of writing.

DISCUSSION

Several trials are currently examining the role of early CCP administration in the treatment of COVID-19 on a therapeutic or prophylactic basis. There are six completed therapeutic trials: two showed clinical benefit- one in high-risk participants who were <72 h from symptom

onset [6]; and the largest outpatient trial (1181 participants) showed benefit in people treated within 8 days of symptom onset [12]. The other trials did not show benefit [10, 11, 13, 14]. In C3PO [10], more participants in the CCP arm were admitted to the hospital directly from the emergency department, which meant they met the primary outcome during their initial visit to the emergency department. This could have skewed the findings with potentially more severely unwell participants in the CCP arm. The first randomized clinical trial exploring post-exposure prophylaxis was halted early as it ceased to be feasible given the availability of vaccination [13]. The trial was too small to assess any effect on progression to severe disease or need for hospitalization.

There are several ongoing studies on early administration of CCP, these trials vary with regards to the timing of CCP administration (96 h–14 days), type of comparative arm used (non-immune plasma, saline, standard of care), patient eligibility (healthy adults to elderly or immunocompromised) and primary outcomes analysed (resolution of SARS-CoV-2 symptoms, hospitalization, adverse events or death). Some of these trials did not specify the volume of CCP administered in the treatment arm. The results of these trials will be important in understanding the role of CCP in treating patients early in their disease course.

Early administration of CCP is associated with different logistical challenges, and OOH/HT of CCP offers a suitable option. Data from clinical trials have shown that early CCP administration is not associated with an increased risk of adverse events compared to other blood components [3–5]. Considering the safety profile of CCP, OOH/HT CCP transfusion is an option for patients who are early in their disease course. Our results showed variation in the availability of OOH/HT programmes. Out-of-hospital transfusion has been in practice for many years in different locations, such as patients' homes, hospices and rehabilitation facilities, and in a variety of patients of different ages and diagnoses [21]. Different reports showed that HT is feasible and safe when performed on selected patients by trained staff under specific protocols [22–24]. The main advantage of this practice is facilitating CCP administration early in the disease course, perhaps before the patients develop their own antibodies. Other potential advantages are facilitating patient-centred care, overcoming the challenges of managing the patients in a busy hospital setting, and ensuring complete post-transfusion follow-up for clinical and laboratory monitoring. It can also be an attractive option to enrol patients in clinical trials and reduce the cost of in-hospital care through the provision of such specialized services in their homes. However, setting up such a programme has been associated with different challenges, as described by the participants of this study that may render the feasibility of initiation of OOH/HT programmes difficult during pandemics.

There are essential components of outpatient transfusion programmes that were reported from HT programmes [21, 22] and more recently from CCP transfusion trials [25]. Considering the required staff expertise and resources, OOH/home CCP transfusion should only be offered in facilities with adequate infrastructure and capacity to manage transfusion-associated adverse events [25]. This is particularly important to ensure recipient safety due to the increased risk because of distance from emergency care. The location of the transfusion should be accessible by ambulance, and the distance or time that it would take to travel to a hospital emergency department should be defined [21, 22]. Establishing temporary facilities, such as annexes from emergency departments or portable treatment facilities, is an option as used in CSSC-001 and CSSC-004 clinical trials [25]. Policies and procedures must be available, and staff training and availability must be considered, with redundancy to cover absences [25]. The enrolment criteria should be specific in enrolling patients who are not acutely ill. Procedures with regard to ABO blood group typing, verification of patient identity and means of access to electronic medical records should be considered [25]. The facility must adhere to all regulations that apply to blood transfusion, including monitoring and reporting transfusion reactions. Instructions should be provided to the patient to report any reactions after the transfusion.

In conclusion, studies are underway on the potential role of early administration of CCP. OOH/HT for early delivery of CCP is attractive in many respects. The results of this international survey identify a number of important practical and logistical challenges that should be addressed in order to ensure the availability of essential resources for an out-of-hospital administration.

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A.Z.R., L.E. and N.R.L. designed the survey and drafted the manuscript; A.Z.R. acquired and analysed the data. Rest of the authors participated in the survey and contributed to the manuscript. We acknowledge experts who participated with details of home transfusion and out-of-hospital CCP availability in their institutions (Appendix S1).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ORCID

Arwa Z. Al-Riyami https://orcid.org/0000-0001-8649-0650
Naomi Rahimi-Levene https://orcid.org/0000-0003-3411-886X
Evan M. Bloch https://orcid.org/0000-0001-8181-9517
Ruchika Goel https://orcid.org/0000-0001-9653-9905
Jean-Baptiste Thibert https://orcid.org/0000-0002-8721-8357
Dana V. Devine https://orcid.org/0000-0002-9059-0344
Richard R. Gammon https://orcid.org/0000-0002-1175-9579
Silvano Wendel https://orcid.org/0000-0002-1941-7733
Rada M. Grubovic Rastvorceva https://orcid.org/0000-0002-4885-3323
Adaeze Oreh https://orcid.org/0000-0001-9141-8215
Gopal Patidar https://orcid.org/0000-0001-9681-3898
Cynthia So-Osman https://orcid.org/0000-0003-4151-2865

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

Plasma transfusion practices: A multicentre electronic audit

Aditi Khandelwal[1,2] | Leigh Minuk[3] | Yang Liu[4] | Donald M. Arnold[4,5] | Nancy M. Heddle[4,6] | Rebecca Barty[4,7] | Cyrus Hsia[8,9,10] | Ziad Solh[8,9,10] | Nadine Shehata[2,11] | Troy Thompson[7] | Alan Tinmouth[12,13] | Iris Perelman[14] | Robert Skeate[1,2] | Amie T. Kron[2,15] | Jeannie Callum[2,16]

[1]Canadian Blood Services, Toronto, Ontario, Canada

[2]The University of Toronto Quality in Utilization, Education and Safety in Transfusion (QUEST) Research Program, Toronto, Ontario, Canada

[3]Department of Internal Medicine, University of Toronto, Toronto, Ontario, Canada

[4]McMaster Centre for Transfusion Research (MCTR), McMaster University, Hamilton, Ontario, Canada

[5]Division of Hematology and Thromboembolism, Department of Medicine, McMaster University, Hamilton, Ontario, Canada

[6]Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario, Canada

[7]Ontario Regional Blood Coordinating Network (ORBCoN), Toronto, Ontario, Canada

[8]Department of Medicine, Western University, London, Ontario, Canada

[9]Department of Pathology and Laboratory Medicine, Western University, London, Ontario, Canada

[10]Transfusion Medicine Laboratories, London Health Sciences Centre, London, Ontario, Canada

[11]Department of Laboratory Medicine and Pathology, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada

[12]Ottawa Hospital Centre for Transfusion Research, Ottawa Hospital and Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

[13]Division of Hematology, Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada

[14]Ottawa Hospital Research Institute (OHRI), Ottawa, Ontario, Canada

[15]Precision Diagnostics and Therapeutics Program, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

[16]Department of Pathology and Molecular Medicine, Kingston Health Sciences Centre, Queen's University, Kingston, Ontario, Canada

Correspondence
Jeannie Callum, Department of Pathology and Molecular Medicine, Kingston Health Sciences Centre, 201b, 88 Stuart Street, Kingston, ON K7L 2V7, Canada.
Email: jeannie.callum@kingstonhsc.ca

Funding information
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Abstract

Background and Objectives: Plasma is often transfused to patients with bleeding or requiring invasive procedures and with abnormal tests of coagulation. Chart audits find half of plasma transfusions unnecessary, resulting in avoidable complications and costs. This multicentre electronic audit was conducted to determine the proportion of plasma transfused without an indication and/or at a sub-therapeutic dose.

Methods: Data were extracted on adult inpatients in 2017 at five academic sites from the hospital electronic chart, laboratory information systems and the Canadian Institute for Health Information Discharge Abstract Database. Electronic criteria for plasma transfusion outside recommended indications were: (1) international normalized ratio (INR) < 1.5 with no to moderate bleeding; (2) INR ≥ 1.5, with no to mild bleeding and no planned procedures; and (3) no INR before or after plasma infusion. Sub-therapeutic dose was defined as ≤2 units transfused.

Results: In 1 year, 2590 patients received 6088 plasma transfusions encompassing 11,490 units of plasma occurred at the five sites. 77.7% of events were either outside indications or under-dosed. Of these, 34.8% of plasma orders had no

indication identified, and 62% of these occurred in non-bleeding patients and no planned procedure with an isolated elevated INR. 70.7% of transfusions were under-dosed. Most plasma transfusions occurred in the intensive care unit or the operating room. Inter-hospital variability in peri-transfusion testing and dosing was observed.

Conclusion: The majority of plasma transfusions are sub-optimal. Local hospital culture may be an important driver. Electronic audits, with definitions employed in this study, may be a practical alternative to costly chart audits.

Keywords

coagulation factor therapy, haemostasis, plasma transfusion

Highlights

- Unnecessary plasma transfusion continues to be a pervasive issue.
- A majority (78%) of plasma transfusions occur either without a guideline-supported indication or at a sub-therapeutic dose.
- To increase the optimal use of plasma, better understanding of local hospital culture and challenges in specific settings, particularly intensive care and operating rooms, is required.

INTRODUCTION

Plasma is a commonly transfused blood product in hospitalized patients. The indications for plasma use include to treat active bleeding or to prevent bleeding after invasive procedures in patients with acquired coagulation factors deficiencies, as detected by abnormal laboratory tests of coagulation [1]. Guidelines advocate for restrictive plasma use; plasma is recommended for patients with active bleeding and markedly abnormal tests of coagulation (international normalized ratio [INR] > 1.5–1.9) or undergoing high-risk invasive procedures and INR > 1.5–1.8 [2–8]. Guidelines emphasize that plasma use for mild elevations in the INR (defined as <1.5–1.9) is ineffective and exposes the patient to harm [5, 8–12]. These guidelines, although widely accepted, are based on mostly small randomized controlled trials in a broad range of patient population leaving considerable uncertainty regarding the benefit–risk profile of plasma transfusion [13].

Chart audits have shown that approximately half of plasma use is sub-optimal [5, 11, 12, 14]. The Canadian plasma transfusion audit data are consistent with data from the United States and the United Kingdom, suggesting sub-optimal plasma use is a common healthcare problem around the world [14–17].

Plasma transfusion can lead to adverse transfusion reactions including transfusion-associated circulatory overload (TACO) and transfusion-related acute lung injury (TRALI) [18–21]. TACO and TRALI are currently the leading causes of transfusion-related fatalities [21–24]. In patients with shock, plasma use is associated with higher rates of ventilator-associated pneumonia and sepsis [24, 25]. In surgical patients, plasma use is associated with a higher risk of bleeding, need for mechanical ventilation and mortality [25, 26]. From a resource stewardship perspective, unnecessary plasma transfusion is associated with a steep increase in healthcare costs [27]. Moreover, use of plasma for transfusion prevents its use to manufacture plasma-derived protein products, including immune globulins [28]. Canada is only able to supply 10%–20% of the source plasma required to manufacture plasma-derived protein products, with the remaining source plasma derived from paid donors in the United States. This reliance on US-plasma is similar to other countries, highlighting a global need to reduce unnecessary plasma transfusions and ensure an ethical and safe supply of fractionated blood products [29].

We electronically audited the appropriateness of plasma use with a large electronic dataset containing patient-level data from five academic centres, encompassing eight hospital sites. The results will be utilized to inform future interventional quality improvement studies at the participating sites to optimize plasma use and to determine the need for expensive and time-consuming manual chart audits.

MATERIALS AND METHODS

We conducted a multicentre retrospective audit of all hospitalized patients, 18 years of age or older, who received one or more units of plasma between 1 January 2017 and 31 December 2017 at five multi-site institutions across Ontario: Sunnybrook Health Sciences Centre, Hamilton Health Sciences, London Health Sciences Centre, The Ottawa Hospital and Mount Sinai Health System. The study was approved by a centralized Research Ethics Board. Individual patient consent was not required as all data were de-identified before analysis.

Patients who received one or more units of plasma were identified through the hospital blood bank information systems. Admissions to hospital were ascertained through the administrative database Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) by hospital file number.

Plasma transfusions were identified as inpatient transfusions if they met either of the following criteria: issued during inpatient admission; or, within 6 h prior to inpatient admission. Patients who underwent plasma exchange were excluded. Plasma exchange patients were identified by either issue of six or more plasma units and a primary discharge diagnosis code for thrombotic thrombocytopenic purpura and/or apheresis procedure with plasma removal.

Data were extracted from the following electronic data sources: laboratory information system, blood bank information system, CIHI-DAD and the Ontario Transfusion Transmitted Injuries Surveillance System. Each hospital site captured the following information electronically: patient characteristics, patient admission information (admission diagnosis, admission time, time of discharge, in-hospital mortality, length of stay, requirement for intensive care unit admission), blood product utilization (date, number of units), laboratory data (result, date, time), type of procedure conducted during the admission (date, time where available) and complications of transfusion.

Sub-optimal use of plasma was adjudicated as use where an indication was not identified or sub-therapeutic dosing. Any plasma unit issued within 15 min of another unit was grouped as a transfusion event. Appropriateness of plasma use was electronically adjudicated for clinical indication and dose at transfusion event level. Transfusion events outside guideline [1–4, 16, 17] indications were defined as any of the following: (i) INR < 1.5 prior to transfusion (closest result to the plasma event and within 24 h) with no bleeding to moderate bleeding (defined below); (ii) INR ≥ 1.5 within 24 h prior to plasma transfusion event, with no bleeding or mild bleeding and no invasive procedure performed within one calendar day of the plasma transfusion (day of plasma transfusion or day after plasma transfusion); (iii) no INR drawn in the 24 h prior to plasma transfusion event and no INR drawn in the 12 h following the plasma transfusion event. Sub-therapeutic dose for these adult patients was defined as transfused a dose ≤2 units of plasma [6, 9, 10]. One plasma unit was defined as a 250 ml equivalent of plasma. The times for all operative, interventional radiology, and bedside procedures were not available across all sites for all procedures. Therefore, 'within one calendar day' was utilized for categorization of appropriateness, rather than a procedure within 6 h as planned prior to the data extract due to the half-life of the plasma effect on coagulation.

Bleeding was categorized as no to mild, moderate and severe. No to mild bleeding was neither moderate nor severe bleeding. Moderate bleeding was defined as 1 unit of red blood cells (RBC) transfused within 24 h before or after a plasma transfusion event or a 20 g/L drop in the haemoglobin within 24 h before and after the plasma transfusion event. Severe bleeding was defined as 2 or more units of RBC transfused within 24 h before or after a transfusion event.

Data mapping and analysis were performed at the McMaster Centre for Transfusion Research. The a priori statistical analysis plan was finalized before data extraction and analysis. Data for each site were mapped to the data dictionary variables to ensure accurate capture of data elements at the different hospitals. The mapping process was validated prior to analysis. Individual patient identifiers were removed from the dataset at each participating hospital and a unique study identifier assigned before the data were transferred to the site for data analysis.

We used descriptive analysis to describe the prevalence of sub-optimal plasma use, as well as the baseline characteristics and invasive procedures conducted at the time of plasma transfusion. We also describe the temporal trend of INR from before to after the transfusion. Means with standard deviations were reported for continuous variables. Medians with interquartile ranges (IQRs) were reported if data were skewed. Institution E was only able to provide summary statistics (with the same analysis plan performed by institution E) due to lack of research ethics board approval to transfer de-identified data, hence no median (IQR) for the five sites overall could be calculated. Counts and proportions were reported for categorical variables. All data were analysed using SAS 9.4 (Carry, NC, USA) by an independent statistician.

RESULTS

Table 1 outlines the baseline characteristics of patients by hospital site. The average age was 62 ± 17 years and 63% were male. The majority of the cohort required intensive care admission (86.0%) and experienced a severe bleeding episode (transfusion of 2 or more units of RBC; 71.1%). Over the 1-year study period, 6088 transfusion events comprising the transfusion of 11,490 units of plasma occurred at the five sites. This cohort had an in-hospital mortality rate of 24.5%, with 10.3% of the patients dying within 24 hours after the plasma transfusion. The mean length of stay of patients receiving plasma transfusions was 19.7 days, with a mean intensive care length of stay of 10.1 days.

Amongst recipients of plasma, the most common diagnoses at admission were cardiovascular disease in 41.1%, traumatic injury in 18.7% and gastrointestinal disease in 15.3% (Table 1). A total of 2150 procedures were performed within one calendar day of the plasma transfusion event, with the most common procedures were cardiopulmonary bypass (30%), insertion of vascular device (18.3%), percutaneous thoracentesis (7.3%), cardiac catheterization (5.1%) and laparotomy (4.1%). Transfusion of other products was also recorded in those receiving plasma (Table 2). The majority of patients receiving plasma also received RBCs (84.1%) and platelet transfusion (58.5%) during their hospital stay.

Adjudication of plasma use is demonstrated in Table 3. Overall, a sub-optimal plasma use, either lack of a clinical indication or sub-therapeutic dose, was observed for 77.7% of transfusion events (Table 3). Absence of an indication for plasma was observed in 34.8% of transfusion events, ranging from 24.6% to 39.8% at the five sites (Table 3). Amongst events where an indication for plasma use was absent, 62% of the events occurred for an INR ≥ 1.5 with no bleeding or invasive procedures within one calendar day. Sub-therapeutic plasma dose was observed in 70.7% of events with single-unit transfusions accounting for 25.2% of the events. The majority (54.9%) of sub-optimal plasma transfusion events occurred in the intensive care patient population.

TABLE 1 Patient baseline characteristics, location at the time of plasma issue, length of stay and mortality for five hospitals in Ontario, Canada

	Hospital A	Hospital B	Hospital C	Hospital D	Hospital E	Overall
Total number of admissions with plasma transfusions	800	298	768	36	728	2630
Unique patients (*n*)	796	297	749	36	713	2591
% of inpatient admissions with plasma transfusions	2.3	1.0	2.0	0.2	1.4	1.5
Age (years) (mean ± SD)	63.2 ± 16.5	59.4 ± 17.9	60.5 ± 16.9	50.4 ± 16.6	62.4 ± 15.9	61.6 ± 16.7
18–50 years, *n* (%)	161 (20.1)	78 (26.2)	181 (23.6)	18 (50.0)	145 (19.9)	583 (22.2)
51–65 years, *n* (%)	224 (28.0)	96 (32.2)	245 (31.9)	10 (27.8)	236 (32.4)	811 (30.8)
66–80 years, *n* (%)	310 (38.8)	92 (30.9)	270 (35.2)	8 (22.2)	271 (37.2)	951 (36.2)
81 or older, *n* (%)	105 (13.1)	32 (10.7)	72 (9.4)	0 (0.0)	76 (10.4)	285 (10.8)
Sex, *n* (%)						
Male	499 (62.4)	184 (61.7)	485 (63.2)	14 (38.9)	476 (65.4)	1658 (63.0)
Reason for admission, *n* (%)						
Cardiovascular diseases	412 (51.5)	121 (40.6)	280 (36.5)	0 (0.0)	267 (36.7)	1080 (41.1)
Trauma	143 (17.9)	95 (31.9)	135 (17.6)	5 (13.9)	113 (15.5)	491 (18.7)
Gastrointestinal diseases	71 (8.9)	10 (3.4)	141 (18.4)	8 (22.2)	110 (15.1)	340 (12.9)
Cancer	72 (9.0)	39 (13.1)	67 (8.7)	10 (27.8)	66 (9.1)	254 (9.7)
Infectious diseases	27 (3.4)	8 (2.7)	30 (3.9)	2 (5.6)	55 (7.6)	122 (4.6)
Pregnancy	15 (1.9)	9 (3.0)	14 (1.8)	6 (16.7)	20 (2.8)	64 (2.4)
Other[a]	60 (7.5)	16 (5.4)	101 (13.2)	5 (13.9)	97 (13.3)	279 (10.6)
Transfusion metrics						
Total number of plasma transfusion events	1583	578	2170	50	1707	6088
Total plasma units transfused	3546	1394	6402	148	3943	11,490
Number of plasma units received per plasma event (mean ± SD)	2.2 ± 1.3	2.4 ± 1.1	3.0 ± 2.2	3.0 ± 2.2	2.3 ± 2.2	2.5 ± 1.9
Plasma transfusion location, *n* (%)						
ICU only	278 (34.8)	111 (37.2)	252 (32.8)	13 (36.1)	356 (48.9)	1010 (38.4)
OR only	296 (37.0)	96 (32.2)	94 (12.2)	15 (41.7)	51 (7.0)	552 (21.0)
Both ICU and OR	73 (9.1)	19 (6.4)	45 (5.9)	1 (2.8)	36 (5.0)	174 (6.6)
Other	153 (19.1)	72 (24.2)	377 (49.1)	7 (19.4)	285 (39.1)	894 (34.0)
Bleeding status,[b] *n* (%)						
No to mild	42 (5.3)	13 (4.4)	151 (19.7)	3 (8.3)	137 (18.8)	346 (13.2)
Moderate	122 (15.3)	55 (18.5)	136 (17.7)	7 (19.4)	93 (12.8)	413 (15.7)
Severe	636 (79.5)	230 (77.2)	481 (62.6)	26 (72.2)	498 (68.4)	1871 (71.1)
Outcomes, *n* (%)						
In-hospital mortality	187 (23.4)	85 (28.5)	177 (23.0)	7 (19.4)	188 (25.8)	644 (24.5)
24-h mortality after plasma transfusion	93 (11.6)	43 (14.4)	78 (10.2)	4 (11.1)	86 (11.8)	270 (10.3)
ICU admission	726 (90.8)	277 (93.0)	635 (82.7)	31 (86.1)	594 (81.6)	2263 (86.0)
ICU LOS (days) (mean ± SD)	8.9 ± 13.5	11.7 ± 13.9	10.3 ± 12.0	13.1 ± 16.7	10.4 ± 14.9	10.1 ± 13.7
LOS (days) (mean ± SD)	16.2 ± 21.4	20.2 ± 24.5	18.1 ± 20.3	27.2 ± 37.2	24.4 ± 31.6	19.7 ± 25.2

Abbreviations: ICU, intensive care unit; LOS, length of stay; OR, operating room.

[a]Other diagnoses include musculoskeletal disease, genitourinary disease, respiratory diseases and metabolic disease.

[b]No to mild bleeding was neither moderate bleeding nor severe bleeding. Moderate bleeding was defined as 1 unit of red blood cells (RBC) transfused within 24 h before or after a transfusion event or a 20 g/L drop in the haemoglobin within 24 h before and after a transfusion event (for non-RBC transfused patients). Severe bleeding was defined as 2 or more units of RBC transfused within 24 h before or after a transfusion event.

TABLE 2 Transfusion data for in-patient admissions receiving plasma transfusion at five hospitals in Ontario, Canada

	Hospital A	Hospital B	Hospital C	Hospital D	Hospital E	Overall
Plasma						
Total number of admissions with plasma transfusions (*n*)	800	298	768	36	728	2630
Number of plasma units received per admission (mean ± SD)	4.4 ± 5.4	4.7 ± 4.7	8.3 ± 15.1	4.1 ± 3.1	5.4 ± 7.7	5.9 ± 9.9
RBC						
Number of admissions with RBC transfusions, *n* (%)	719 (89.9)	270 (90.6)	582 (75.8)	34 (94.4)	608 (83.5)	2213 (84.1)
Number of RBC units per admission for those transfused (mean ± SD)	8.6 ± 8.4	8.5 ± 8.2	10.2 ± 13.2	10.8 ± 10.2	8.9 ± 9.8	9.1 ± 10.3
PLT						
Number of admissions with PLT transfusions, *n* (%)	521 (65.1)	203 (68.1)	400 (52.1)	10 (27.8)	404 (55.5)	1538 (58.5)
Number of PLT pools per admission for those transfused (mean ± SD)	3.3 ± 5.4	2.6 ± 3.3	3.2 ± 3.8	2.2 ± 2.1	3.5 ± 6.4	3.2 ± 5.1
Cryoprecipitate[a]						
Number of admissions with cryoprecipitate transfusions, *n* (%)	214 (26.8)	116 (38.9)	153 (19.9)	4 (11.1)	92 (12.6)	579 (22.0)
Number of cryoprecipitate units per admission for those transfused (mean ± SD)	17.1 ± 13.9	19.7 ± 37.0	21.2 ± 25.2	15.0 ± 5.8	20.9 ± 24.2	19.3 ± 24.6
Prothrombin Complex Concentrate 500 IU doses						
Number of admissions with PCC use, *n* (%)	17 (2.1)	6 (2.0)	34 (4.4)	3 (8.3)	65 (8.9)	125 (4.8)
Number of PCC 500 IU doses per admission for those given PCC (mean ± SD)	4.2 ± 1.5	3.3 ± 1.6	1.8 ± 1.1	3.7 ± 0.6	4.2 ± 3.1	3.5 ± 2.6

Abbreviations: PCC, prothrombin complex concentrate; PLT, platelet; RBC, red blood cell.
[a]Each unit is from a different donor (all plasma in Ontario provided as single units rather than pre-pooled in groups of 5).

TABLE 3 Adjudication of plasma use events by indication and dose

	Hospital A (*N* = 1583)	Hospital B (*N* = 578)	Hospital C (*N* = 2170)	Hospital D (*N* = 50)	Hospital E (*N* = 1707)	Overall (*N* = 6088)
Plasma use without indication or under-dosed, *n* (%)	1321 (83.4)	412 (71.3)	1569 (72.3)	35 (70.0)	1394 (81.7)	4731 (77.7)
Sub-therapeutic plasma, *n* (%)	1256 (79.3)	387 (67.0)	1340 (61.8)	26 (52.0)	1297 (76.0)	4306 (70.7)
1 unit	347 (27.6)	118 (30.5)	382 (28.5)	8 (30.8)	678 (52.3)	1533 (35.6)
2 units	909 (72.4)	269 (69.5)	958 (71.5)	18 (69.2)	619 (47.7)	2773 (64.4)
Plasma use without indication, *n* (%)	422 (26.7)	142 (24.6)	857 (39.5)	17 (34.0)	679 (39.8)	2117 (34.8)
(a) INR < 1.5 with no to moderate bleeding	131 (31.0)	13 (9.2)	192 (22.4)	8 (47.1)	51 (7.5)	395 (18.7)
(b) INR ≥ 1.5 with no bleeding or invasive procedures	205 (48.6)	119 (83.8)	434 (50.6)	9 (52.9)	546 (80.4)	1313 (62.0)
(c) No INR drawn 24 h before and no INR drawn 1–12 h after plasma infusion	86 (20.4)	10 (7.0)	231 (27.0)	0 (0.0)	82 (12.1)	409 (19.3)

Abbreviation: INR, international normalized ratio.

The pre-transfusion INR was 1.9 ± 1.6 and an overall reduction in INR measured within 6 h of plasma transfusion was 0.4 ± 1.6 (Table 4). A pre-plasma INR measurement not available for 17.8% (0.0%–27.0%) of plasma transfusion events and a pre-plasma INR measurement below 1.5 in 44% (28.2%–58.7%) events (Table 4). There was a wide variability in plasma utilization across the five centres. The plasma units transfused per 100 admissions ranged from 0.73 to 16.44. When benchmarked to RBCs, the use of plasma units transfused ranged from 3.77 to 45.07 per 100 RBC units across the sites. Plasma events classified as lacking a clinical indication ranged across sites from 24.6% to 39.8% (Table 3). Plasma transfusion for no to mild bleeding was seen in 4.4%–19.7% of patients, depending on the site.

TABLE 4 Peri-transfusion INR testing at five hospitals in Ontario, Canada

	Hospital A ($N = 1583$)	Hospital B ($N = 578$)	Hospital C ($N = 2170$)	Hospital D ($N = 50$)	Hospital E ($N = 1707$)	Overall ($N = 6088$)
Pre-transfusion INR available, *n* (%)	1318 (83.3)	519 (89.8)	1782 (82.1)	49 (98.0)	1335 (78.2)	5003 (82.2)
Post-transfusion INR available, *n* (%)	1030 (65.1)	452 (78.2)	1406 (64.8)	10 (20.0)	1118 (65.5)	4016 (66.0)
Pre-transfusion and post-transfusion INR available, *n* (%)	863 (54.5)	403 (69.7)	1269 (58.5)	9 (18.0)	873 (51.1)	3417 (56.1)
Pre-transfusion INR (mean ± SD)	1.7 ± 2.0	2.0 ± 1.6	1.8 ± 1.4	1.4 ± 0.3	2.2 ± 1.6	1.9 ± 1.6
≤1.49, *n* (%)	774 (58.7)	178 (34.3)	842 (47.3)	33 (67.3)	376 (28.2)	2203 (44.0)
1.50–1.79, *n* (%)	257 (19.5)	120 (23.1)	399 (22.4)	9 (18.4)	336 (25.2)	1121 (22.4)
≥1.80, *n* (%)	287 (21.7)	221 (42.6)	541 (30.4)	7 (14.2)	623 (46.7)	1679 (33.6)
Post-transfusion INR (mean ± SD)	1.4 ± 1.3	1.4 ± 0.4	1.4 ± 0.7	1.3 ± 0.1	1.6 ± 0.7	1.4 ± 0.9
≤1.49, *n* (%)	823 (79.9)	304 (67.3)	962 (68.4)	9 (90.0)	587 (52.5)	2685 (66.9)
1.50–1.79, *n* (%)	122 (11.8)	82 (18.1)	238 (16.9)	1 (10.0)	284 (25.4)	727 (18.1)
≥1.80, *n* (%)	85 (8.3)	66 (14.6)	206 (14.7)	0 (0.0)	247 (22.1)	604 (15.0)
Post-transfusion INR reduction (mean ± SD)	0.3 ± 2.1	0.5 ± 1.3	0.4 ± 1.4	0.1 ± 0.3	0.5 ± 1.4	0.4 ± 1.6

Abbreviation: INR, international normalized ratio.

DISCUSSION

In this multicentre, retrospective electronic audit of plasma transfusion across five academic institutions, we observed that one-third of plasma transfusions were given without clear indication based on our electronic criteria and over 70% of patients were transfused a sub-optimal dose. Inadequate coagulation testing both before and after plasma transfusion was also observed at all sites. Plasma use outside guideline-based indications in the inpatient setting is likely contributing to increased costs to our health systems [27] and exposes patients to potential harm [19].

We found a similar rate of sub-optimal plasma use as previous audits [5, 17, 30–32]. In 2007, a retrospective, manual chart audit in Canada, showed unnecessary plasma transfusion in 45% [5] and an audit across intensive care units in Australia and New Zealand identified 26% of plasma was administered to patients with INR < 1.5 [3]. A recent audit demonstrated that 48.6% of plasma transfusions occur without an indication [15]. Previous audits sampled a small number of charts from each hospital. However, this large database-powered multicentre audit allowed sampling of consecutively transfused patients and a greater number of patients with minimal costs, improving the accuracy of the estimates.

A sub-therapeutic dose was administered in 71% of plasma events. This is higher than previously reported 42.4% in a 2013 audit [5]. In our study, approximately 25% of these were single-unit transfusions. Another recent single-centre audit demonstrated that up to 40% of their plasma transfusions are single-unit [15]. Of these, 24.3% (range 16%–28.9%) were also given outside a clinical indication. It is possible that the transfusion of 1 or 2 units of plasma may be an unintended effect of efforts to promote single-unit RBC transfusions, with slogans such as 'why give two when one will do' [5, 33]. A lower dose may also be transfused due to an adverse reaction or volume overload, achievement of haemostasis prior to full dose completion, or a failure in knowledge translation to the bedside physician. Our electronic audit was unable to capture the frequency of issued and returned units of plasma (e.g. 4 units ordered, 1 transfused and 3 returned).

Plasma is often transfused as prophylaxis for non-bleeding patients with an abnormal INR. Even though INR levels have been used to guide plasma transfusion in the setting of procedures, a mildly abnormal INR does not predict bleeding complications [34–36]. A study of 121 patients with INR 1.1–1.85 demonstrated that plasma transfusion corrected the INR in only 0.8% of cases and the INR only decreased by 0.07 [9]. The effect of plasma on the INR was strongest for INR over 2 and minimally effective for correcting INR less than 1.7 [37]. The standard dose of plasma is 4 units for a 70 kg individual (15 ml/kg) [4], which may only be expected to decrease the INR by 6% [34]. The conclusion of these large observational studies is that plasma should not be used to correct prolonged INR in absence of bleeding, unless INR is substantially elevated (>1.8) in preparation for high-risk for bleeding procedures [7, 38].

In patients with bleeding, the most common diagnosis was cardiovascular disease. In cardiac surgery patients experiencing severe bleeding, systematic review and meta-analysis of 17 trials encompassing over 8000 patients assessing point-of-care-testing thromboelastometry (ROTEM) guided transfusion therapy has shown decreased odds of blood product use [39]. In addition, a multicentre, cluster randomized trial involving over 7400 cardiac surgery patients found ROTEM reduced the risk of transfusion and major bleeding [40]. A recent observational study of ROTEM-guided transfusion algorithm in the cardiovascular surgery patients also showed a 12% reduction in plasma use [41]. Perhaps, wider adoption of viscoelastic-guided transfusion therapy may increase appropriate plasma use [42]. The INR was not measured before the plasma event in 18% of patients (and

ranged across sites from 2% to 23%) suggesting that point-of-care-testing may assist with improving plasma transfusion practice. Measurement of the INR after infusion was much less common (missing in 34% and ranging from 22% to 80% across the sites) and suggests room for improvement in patient care.

Limitations of this retrospective, observational study include the dependence on a database that relies on accurate coding for primary diagnosis and procedures at each hospital site by trained coders. Although the CIHI-DAD has been shown to be highly reliable database [43, 44], some bedside invasive procedures may have been missed. The standard dose of 15 ml/kg, approximately 4 units in an adult, is based on laboratory studies demonstrating a 20% increase in clotting factors rather than bleeding as an outcome [4]. If replacing low clotting factors, a smaller dose is likely to have minimal benefit. Our electronic definition for bleeding severity may have failed to capture patients with critical location bleeding without transfusion, such as intracranial haemorrhage, if this diagnosis was not coded in CIHI-DAD. Moreover, it is possible that plasma was being utilized for volume expansion explaining why plasma was transfused to patients with normal or without measured INRs [45, 46]; however, guidelines explicitly state not to use plasma for this indication and further studies are required to establish this as an indication [45, 46]. INR values and testing times were extracted from the laboratory information system and hence it is possible that the physician ordering plasma may not have been aware of the INR results at the time of the infusion of the plasma. It is possible that some post-infusion INR testing were not indicated in all plasma transfusions, for example a patient after cardiovascular surgery with mildly elevated INR pre-transfusion and adequately haemostasis post-infusion. Diagnosis of trauma was recorded in only 20% of cases, hence ratio-based resuscitation in trauma was likely not a significant contributor to plasma use outside guideline-based indications in this study as this small proportion would likely have been classified as 'severe bleeding' with two or more RBCs transfused.

The strengths of this study include capturing a large number of consecutive plasma transfusion events across multiple institutions, where the data were extracted in a consistent manner across sites with added information regarding timing of transfusions and the date on which procedures were performed. In addition, our findings are concordant with prior plasma audits in adults and children at academic and non-academic centres [5, 18, 47, 48]. As such, this approach to a digital audit is likely generalizable to other institutions. Moreover, to mitigate the risk of over-classifying plasma transfusion use as outside indication, the electronic bleeding definitions were intentionally liberal (2 units transfused in the 24 h before or after the plasma event for severe bleeding) and procedures within one calendar day of plasma transfusion (rather than within 6 h) were captured. It is likely that rates of plasma transfusion without an indication are likely higher than reported here if a manual chart audit could have been done on these 6088 plasma events. Our electronic criteria need validation at other sites to determine generalizability outside of our jurisdiction.

Clinical plasma transfusion decisions may be guided by historical practices and institutional culture [49], rather than evidence and guidelines. Considerable inter-hospital variability in plasma use and pre-transfusion INR thresholds suggests that local hospital culture may be a driver of plasma use (sub-optimal and optimal). Future studies should include the collection of qualitative and quantitative data from evaluations targeted towards the areas of the hospital with the highest burden of sub-optimal plasma use. These may include targeted interviews with critical care physicians and prospective audits of plasma orders to provide more in depth understanding of the drivers for the lack of adherence of plasma transfusion practice to published guidelines.

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CONFLICT OF INTEREST

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ORCID

Aditi Khandelwal https://orcid.org/0000-0002-5585-6194
Ziad Solh https://orcid.org/0000-0002-1518-1831
Alan Tinmouth https://orcid.org/0000-0001-8869-389X
Amie T. Kron https://orcid.org/0000-0001-6315-5315

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ORIGINAL ARTICLE

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Extracorporeal photopheresis in paediatric patients: A retrospective comparison between different 'off-line' protocols

Elena Sebastián[1,2] | Eva María Andrés Esteban[2,3] | Marta González-Vicent[1] | Jesús González de Pablo[2] | Josune Zubicaray[1,2] | Eva Gálvez[1] | María Guillén[4] | Julia Ruiz Pato[1] | Blanca Molina[1] | Gustavo Albi[5] | Manuel Ramírez[6] | Ana Castillo[6] | Florencio Pérez Maroto[6] | Luis Madero[1] | Miguel Ángel Díaz[1] | Julián Sevilla[1,2]

[1]Onco-Hematology Department, Hospital Infantil Universitario Niño Jesús, Madrid, Spain

[2]Fundación Investigación Biomédica Hospital Infantil Niño Jesús (FIBHINJ), Madrid, Spain

[3]Applied Economics Department, Universidad Rey Juan Carlos, Madrid, Spain

[4]Hematology Department, Hospital Universitario Miguel Servet, Zaragoza, Spain

[5]Radiology Department, Hospital Infantil Universitario Niño Jesús, Madrid, Spain

[6]Hematology and Oncology Laboratory, Hospital Infantil Universitario Niño Jesús, Madrid, Spain

Correspondence
Elena Sebastián, Hospital Infantil Universitario Niño Jesús, Madrid, Spain.
Email: elena.sebastian@salud.madrid.org

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Abstract

Background and Objectives: Extracorporeal photopheresis (ECP) has been shown to be an effective treatment for graft-versus-host disease (GvHD). However, information regarding lymphocyte collection for ECP in children is limited. The aim of this study was to analyse and compare lymphocyte collection for ECP in children using different devices and protocols. Moreover, we have studied both safety and variables of the infused product related to treatment efficacy.

Patients and Methods: This was a retrospective study of 91 patients who underwent 1524 apheresis procedures with either the COBE Spectra or Spectra Optia system. The comparison study between the Optia protocols (MNC and CMNC) was prioritized. We analysed 578 procedures using the Optia blood cell separator: 204 and 374 using the MNC and the CMNC protocol, respectively.

Results: The Optia CMNC protocol showed better collection efficiency, with increased lymphocyte collection per kg of body weight ($p < 0.001$). On multivariate analysis, the type of protocol showed no relationship with haematocrit or platelet loss. Most procedures were well-tolerated, with the most frequent adverse events related to venous access (21.7%). Seventy-one percent of patients had either partial or complete clinical GvHD response. In the multivariate model, only two variables were associated with a better response to ECP, younger age and a greater increase of B lymphocytes after treatment.

Conclusion: Lymphocyte collection for ECP is well-tolerated in most children, achieving complete or partial response in more than half of GvHD patients. CMNC is the optimal software to perform lymphocyte collection in children.

Keywords

COBE, extracorporeal photopheresis, GvHD, Optia, paediatric patients

Highlights

- We report here the largest series of paediatric patients undergoing off-line extracorporeal photopheresis (ECP) for graft-versus-host disease (GvHD) where the CMNC and MNC Optia protocols for mononuclear cell (MNC) collection were compared.
- Use of the Optia blood cell separator with the CMNC program was more efficient than its use with the MNC program for collection of MNC for ECP.
- ECP treatment was associated with a complete or partial response in more than half of GvHD patients. Younger patient age and a greater increase in B lymphocytes after treatment were associated with a better response to ECP.

INTRODUCTION

Extracorporeal photopheresis (ECP) is a cellular therapy that uses apheresis to collect white blood cells for subsequent exposure to 8-methoxypsoralen (8-MOP) and ultraviolet A (UVA) light followed by reinfusion into the patient. In recent years, ECP has been used as a second-line treatment in adult and paediatric patients with graft-versus-host disease (GvHD) [1], and it has been proven efficient in both acute and chronic GvHD [2]. The mechanism of action is not well understood, though it seems to modify the biologic response by deleting graft-reactive T cells and increasing regulator T lymphocytes and natural killer cells [3, 4], which causes a shift from an inflammatory state to immune tolerance [4].

Since 1980, ECP has been primarily used in adults with cutaneous T cell lymphoma (CTCL) [5]; ECP was then expanded to other immunological diseases such as chronic GvHD (cGvHD) in 1994 [6] and then to acute GvHD in 1998 [7]. The first studies in children were published in the 1990s (cGvHD [8, 9] and aGvHD [10]). The response rates reported in paediatric patients are between 50% and 100% in aGvHD (depending on the organ) [2] while cGvHD patients have a 60% response rate [2]. However, there are no clinical trials in children and no markers to predict efficacy [2].

Apheresis technology was designed for adult patients, and performing the procedure in children presents several challenges such as securing proper vascular access for a sufficient flow rate. Additionally, haematologic and metabolic parameters require close monitoring. Prolonged apheresis can also limit the viability of the procedure in children due to its psychological impact. Regarding ECP specifically, children enrolled in ECP programmes present GvHD and tend to have only a fair overall condition, with lower pre-apheresis complete blood count, mainly in acute GvHD. It is therefore essential that these children with GvHD receive treatment with an optimal apheresis device to efficiently obtain an ample number of mononuclear cells (MNC) and low loss of haematocrit and platelets.

Published data on the use of ECP in children are limited and previous studies have been carried out with small sample sizes [4]. It is widely accepted that there are no absolute contraindications for ECP on account of low white blood counts or thrombocytopenia, and there is also widespread agreement on the importance of the device. Furthermore, most authors consider that ECP is safe, eliciting a good response in children and that it is important that the procedure be performed by a specialized team. However, there are scant data on adverse events and tolerance, procedure length, processed volume and efficiency with the different apheresis devices and protocols, and there are few markers capable of predicting treatment response.

To date, the only data published on children undergoing ECP with the new Optia device have appeared in isolated case reports. Moreover, regarding non-mobilized leukocytapheresis in children, there are no studies in children comparing the two different Optia protocols, neither concerning photopheresis nor immunotherapy. Even-Or et al. compared non-mobilized leukocytapheresis with Optia MNC versus COBE Spectra in children for immunotherapy, finding the Optia MNC to be more efficient and as safe as the COBE device [11].

Given the promising results of chimeric antigen receptor (CAR)-transfected T cells therapy, MNC collection procedures in children are increasing and are expected to increase further in the near future. Therefore, it is interesting to know which is the best machine to perform leukocytapheresis in children, not only for patients in a photopheresis programme, but also for those who require CAR-T immunotherapy.

In this study, performed in a single centre with extensive experience in ECP and GvHD [3, 12], we analysed the largest series of paediatric patients undergoing 'off-line' ECP published to date, focusing on safety, clinical response and device comparison. This is the first study comparing the efficiency of lymphocyte collection between two currently available automated ECP protocols, MNC and CMNC Optia (working with intermittent and continuous-flow collection, respectively) in children undergoing ECP.

PATIENTS AND METHODS

The study was performed in accordance with local ethics committee guidelines and in agreement with the Declaration of Helsinki. Written informed consent to undergo the procedure and for use of the recorded data was obtained from each patient and/or a family member. Data were anonymized.

Study design

The aims of this retrospective study were as follows:

1. To analyse the main adverse events in children undergoing ECP.

2. To compare the two programs available with the Spectra Optia device (MNC and CMNC) in a paediatric population undergoing ECP to determine which is more efficient and could be expanded to lymphopheresis for CAR-T therapy.
3. To analyse the relationship between the variables related to the infused product and the treatment efficacy.

We have included all the ECP procedures performed in our centre from September 2006 to November 2019.

Safety

Adverse events were evaluated following the Hemapheresis Committee of the American Association of Blood Banks questionnaire [13] in all the leukocytapheresis procedures ($n = 1524$). Some adverse events considered physiological according to this questionnaire, such as mild paresthesias or mild vasovagal events, were also considered in the present series. We have also included some aspects such as need to change access/return, need to flush the catheter, need to use of urokinase, haematoma or pain not included in the cited questionnaire. Adverse events related to photopheresis collection were recorded prospectively by the nurses in the worksheet for every procedure.

ECP procedures

We have included all the apheresis procedures from September 2006 to November 2019 in which we had the data to perform the analysis ($n = 1517$).

All collections were performed with an 'off-line' method. Apheresis procedures for MNC collection were performed either with the COBE Spectra or Spectra Optia system. Initially, we used COBE Spectra (Terumo BCT, Lakewood, CO) on either the AutoPBSC: 6.1 PBSC or CMNv7 program. More recently, we switched to the Spectra Optia device (Terumo BCT), using either the MNC2 or CMNC program. For these procedures, the team of nurses followed device- and protocol-specific manufacturer instructions.

The applied settings in Spectra Optia to collect the lymphocytes are as follows: flush and chase volumes of the MNC program were set at 16 ml and 4 ml, respectively. For CMNC procedures, collection pump flow rate was set at 1 ml/min and collection preference was adjusted to a collection line haematocrit of 2%.

Before all the procedures, a complete blood count, biochemistry and coagulation tests were performed in each patient. If the patient had two courses, these tests were performed before each course, and then before and after each procedure. Furthermore, clinical evaluation of the degree of GvHD of the patient was carried out before each course of photopheresis (and also before the second course in cases where there were two). After each cycle of ECP, clinical response of every patient was evaluated following the response criteria published by Greinix et al. [7]

We usually processed between 1 and 2 blood volumes to collect MNCs. The collected product was diluted to a volume of 300 ml by adding saline, and subsequently 3 ml of 8-MOP aqueous solution (Gerot Pharmaceutika, Vienna, Austria) was added to achieve a final concentration of 200 ng/ml. This final product was then transferred to a UVA-permeable bag (MacoPharma, Tourcoing, France), exposed to UVA irradiation (UVMATIC irradiator, Vilbert Lourmat, France) at a dose of 2 J/cm^2 and immediately reinfused [14]. In patients with body weight <15 kg, the blood cell separator is primed with packed red blood cells, and the final collected product is concentrated to 150 ml. Anticoagulant citrate dextrose formula-A is used as an anticoagulant at a ratio of 14/1 or 12/1. Intravenous calcium is usually used as prophylaxis as per institutional protocol.

Collection efficiency (CE) was calculated using the following formulas:

$$\text{CE1}(\%) : \text{product total lymphocytes}/(\text{pre} - \text{apheresis} + \text{post} - \text{apheresis lymphocytes}/2) \times \text{processed volume}$$

$$\text{CE2}\,(\%) : \text{product total lymphocytes}/\text{pre} - \text{apheresis lymphocytes} \times \text{processed volume}$$

$$\text{Platelet loss} : 100 - (\text{platelet count after the collection} \times (100/\text{platelet count before collection}))$$

$$\text{Haematocrit loss} : \text{pre} - \text{collection haematocrit} - \text{post} - \text{collection haematocrit.}$$

Clinical assessment

Ninety-one patients diagnosed with acute or chronic GvHD were included from September 2006 to November 2019. Histological examination was performed in all cases, mainly in the skin.

Clinical response was considered evaluable if a patient had at least two sessions for acute GvHD or eight sessions for those treated for chronic GvHD. Patients were evaluated weekly in acute GvHD and monthly in chronic GvHD. Clinical response was defined following the criteria published by Greinix et al. [7] Complete response was defined as resolution of all organ manifestations. Partial response was defined as greater than 50% response of organ involvement. Absence of response was defined as stable or progressively worsening GvHD and/or the inability to taper other medication by at least 50%.

According to our protocol, ECP sessions were performed twice a week (consecutive days) for 4 weeks, followed by 2 consecutive days every 2 weeks for 3 months or until clinical improvement for acute GvHD. Patients with chronic GvHD were given ECP on 2 consecutive days (one cycle) at 2-week intervals for 6 months or until maximum response. Progressive tapering of immunosuppressive therapy and discontinuation of ECP depended on clinical response, which was defined according to previously published criteria [7].

Total leukocytes or lymphocytes infused per kilogram of body weight and median number of leukocytes or lymphocytes per infusion

TABLE 1 Demographic characteristics, pre- and post-collection blood count results, and apheresis parameters between patients undergoing procedures with the Optia CMNC versus MNC apheresis devices

Variable	Optia CMNC ($n = 374$)	Optia MNC ($n = 204$)	p value
Patient demographics			
Age (years)	11.53 ± 5.04	10.61 ± 5.54	0.064
Weight (kg)	38.49 ± 20.85	35.59 ± 16.92	0.090
Blood results PRE-collection			
Haematocrit (%)	32.58 ± 4.99	33.56 ± 4.07	0.045
Leukocytes ($\times 10^6$/ml)	6.45 ± 0.24	5.74 ± 0.25	0.056
Lymphocytes ($\times 10^6$/ml)	0.91 ± 0.05	1.08 ± 0.09	0.087
Platelets ($\times 10^6$/ml)	113.82 ± 4.45	146.65 ± 8.89	0.001
Apheresis parameters			
TBV processed (fold)	1.82 ± 0.02	1.82 ± 0.02	0.665
Time (min)	162.32 ± 1.62	168.80 ± 2.36	0.021
Blood results POST-collection			
Haematocrit (%)	31.51 ± 0.25	31.86 ± 0.28	0.380
Leukocytes ($\times 10^6$/ml)	6.87 ± 0.27	5.99 ± 0.26	0.061
Lymphocytes ($\times 10^6$/ml)	0.89 ± 0.05	0.95 ± 0.07	0.468
Platelets ($\times 10^6$/ml)	87.45 ± 5.16	102.44 ± 7.39	0.091

Note: Data are presented as mean and SD.
Abbreviation: TBV, total blood volume.

were correlated with the clinical response to find predictors of clinical benefit.

The total number of different blood cell populations in peripheral blood was analysed before and after the procedures to study significant changes that may aid in understanding the physiopathology of this approach.

Statistics

Quantitative data were described using mean and standard deviation (SD), and qualitative data through its distribution function. For comparisons between devices and programs, the Student's t test was used for numerical data and the chi-square test was used in other cases. The relationship between pre-lymphocytes and total lymphocytes/kg in apheresis was measured by means of linear regression stratified according to the protocol selected. The goodness-of-fit of the regression model was performed using the R^2 coefficient.

For efficiency measures, a mixed linear regression model with the maximum-likelihood estimation method was used, where each of the efficiency parameters included in the study were introduced as dependent variables, and factors such as type of ECP, age, weight, pre-apheresis levels of lymphocytes/haematocrit/platelet in blood or TBV were processed as independent variables; ECP type was considered a fixed variable and all other variables were considered mixed. The model is presented only with those variables that were statistically significant, showing the coefficient value and its 95% confidence interval (CI).

To analyse the response, multivariate analysis was performed using binary logistic regression with the forward conditional method. The dependent variable was response (yes/no) and independent variables were all variables that were statistically significant on bivariate analysis or for which there was a plausible clinical implication. The dependent variables were age, weight, conditioning regimen, type of donor, thrombocytopenia after transplant, microangiopathy, type of GvHD, presence of adverse events associated with ECP and B lymphocyte difference (post-pre). Calibration of the model was performed using the Hosmer–Lemeshow test. Discriminatory power was assessed using the area under the receiver-operating characteristics (ROC) curve obtained by analysing the probability of the value predicted by the multivariate model. The results of the multivariate model were adjusted, and we present the corresponding odds ratio and its 95% CI.

Data were collected using Microsoft Excel 2010 (Microsoft Corporation, Redmond, Washington, USA) and FileMaker 5 (FileMaker, Inc. Santa Clara, California, USA). Statistical analysis was carried out with the SPSS Statistics 22.0 program (IBM, Armonk, New York, USA) and p values <0.05 were considered significant.

RESULTS

Patients and ECP procedures

Safety data were collected on all leukocytapheresis procedures ($n = 1524$). A total of 1517 ECP procedures were included in the analysis comparing devices and programs: 71 were performed with the COBE AutoPBSC 6.1, 868 with the COBE Spectra CMNv7, 204 with the Optia MNC2 and 374 with the Optia CMNC.

TABLE 2 Comparison between the Optia CMNC and MNC apheresis devices with regard to the collection product and performance parameters

Variable	Optia CMNC ($n = 374$)	Optia MNC ($n = 204$)	p value
Product parameters			
Product volume (ml)	125.29 ± 30.42	37.41 ± 25.41	0.001
Leukocytes ($\times 10^6$/ml)	36.62 ± 1.61	65.18 ± 2.81	0.001
Total product leukocytes ($\times 10^6$)	4686.21 ± 227.72	2328.70 ± 130.52	0.001
Leukocytes/kg ($\times 10^6$)	135.69 ± 5.81	71.49 ± 3.67	0.001
Lymphocytes ($\times 10^6$/ml)	16.27 ± 1.14	27.76 ± 1.91	0.001
Total product lymphocytes ($\times 10^6$)	2124.74 ± 165.85	1029.85 ± 93.60	0.001
Lymphocytes/kg ($\times 10^6$)	60.24 ± 3.57	33.56 ± 2.74	0.001
Haematocrit (%)	2.45 ± 0.06	6.05 ± 0.28	0.001
Platelets ($\times 10^6$/ml)	614.78 ± 23.38	1148.73 ± 74.22	0.001
Performance parameters			
CE 1	52.11 ± 1.47	29.05 ± 1.48	0.001
CE 2	55.56 ± 1.89	29.69 ± 1.60	0.001
Haematocrit loss (%)	1.28 ± 0.19	1.70 ± 0.23	0.183
Platelet loss (%)	13.66 ± 2.55	23.46 ± 2.90	0.015
Sensitivity analysis. Comparison by eliminating the smallest 10% of CE1 and CE2			
	Optia CMNC ($n = 341$)	**Optia MNC ($n = 174$)**	**p value**
Product parameters			
Product volume (ml)	126.03 ± 30.49	39.25 ± 26.03	0.001
Leukocytes ($\times 10^6$/ml)	36.94 ± 3.13	68.28 ± 3.76	0.001
Total product leukocytes ($\times 10^6$)	4765.27 ± 442.35	2546.66 ± 188.33	0.001
Leukocytes/kg ($\times 10^6$)	135.37 ± 10.87	77.00 ± 5.52	0.001
Lymphocytes ($\times 10^6$/ml)	17.31 ± 2.19	30.15 ± 2.66	0.001
Total product lymphocytes ($\times 10^6$)	2265.84 ± 317.15	1155.88 ± 138.38	0.001
Lymphocytes/kg ($\times 10^6$)	64.07 ± 6.78	36.66 ± 3.95	0.001
Haematocrit (%)	2.47 ± 0.09	5.82 ± 0.29	0.001
Platelets ($\times 10^6$/ml)	629.33 ± 44.73	1213.29 ± 105.92	0.001
Performance parameters			
CE 1	55.69 ± 2.54	33.00 ± 2.02	0.001
CE 2	59.28 ± 3.37	33.54 ± 2.23	0.001
Haematocrit loss (%)	1.28 ± 0.38	1.79 ± 0.33	0.141
Platelet loss (%)	13.52 ± 2.68	23.39 ± 3.20	0.025

Note: Data are presented as mean and SD and compared between blood cell separators.
Abbreviation: CE, collection efficiency.

The average time of collection was 157 min.

Safety: adverse events

The adverse events were recorded in all the leukocytapheresis procedures ($n = 1524$). The most frequent collection-related adverse events concerned venous access in 329 (21.7%). Most procedures (930 of them, which represents 61%) were performed using a catheter placed in the femoral vein followed by the jugular (19.9%); only 8.1% of procedures were performed through peripheral veins. The catheter-related adverse events recorded were as follows: need to change return/access line in 214 of 329 procedures (65%); catheter flushing in 165 procedures (50.5%); use of urokinase anticoagulation to achieve the adequate flow rate in 104 (31.6%); infection in 48 (14.5%); and haematoma or pain in 10 (3%).

Only one patient developed severe hypotension and fever (most likely secondary to infection). Additionally, citrate toxicity was recorded in 6.2% of all procedures, causing episodes of paraesthesia, nausea or vomiting related to mild hypocalcaemia. Median levels of

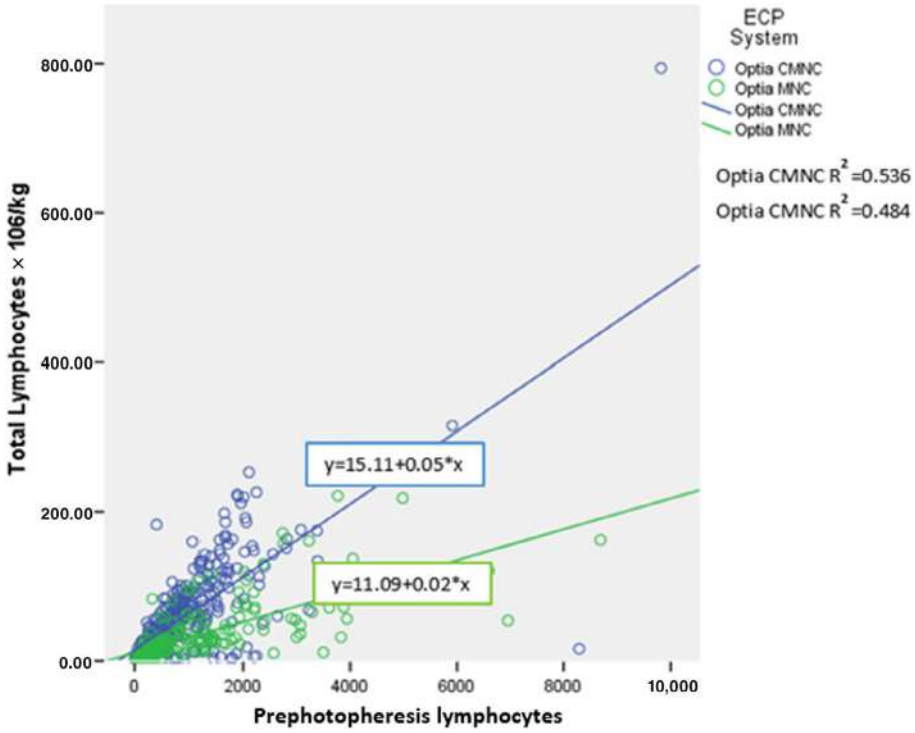

FIGURE 1 Correlation between lymphocyte counts in peripheral blood before collection and total lymphocytes collected per patient body weight. Each circle represents a procedure. Total lymphocytes $\times$ 10^6 versus pre-photopheresis lymphocytes. Blue: Optia CMNC system. Green: Optia MNC system

haematocrit and platelet loss were 2.9% (0.7–4.7) and 28.6% (15.7–39.2), respectively. Transfusion support consisted of packed red blood in 20.1% of collections and platelet support in 11.8%. However, it is important to mention that most procedures were well-tolerated, and only one required interruption due to an adverse event (severe hypotension and fever as mentioned above).

Comparison of blood cell separators

As the COBE Spectra device is no longer available for clinical use, here we focus on the Optia protocols.

Comparison between Optia MNC and Optia CMNC protocols

We analysed 578 procedures using the Optia blood cell separator: 204 procedures using the MNC program and 374 with the CMNC protocol. Pre-leukocytapheresis characteristics were not different between the two cohorts (Table 1).

CE parameters were all significantly better with the CMNC protocol (Table 2). This is represented by both CE1 and CE2, which were better for CMNC than for MNC, $p < 0.001$ (Table 2). Moreover, CMNC showed better lymphocyte collection per kg of body weight compared with MNC, $p < 0.001$ (Table 2).

Total volume collected and total number of cells were higher with the CMNC program with a less concentrated final product (Table 2). Shorter procedure time and lower platelet loss were observed with the CMNC protocol (Tables 1 and 2). There were no differences in haematocrit loss (Table 2) or transfusions performed with red blood cells or platelets (data not shown).

We repeated the analysis excluding the lowest 10% of CE1 and CE2 values, considering that very small CE values may be associated with inappropriate lymphocyte collection due to instability in layers caused by poor venous access (and loosening of the interface). We can see in Table 2 how even after excluding these values, the relationship remains similar between both devices.

For both programs, there was a linear correlation between pre-collection lymphocyte counts in peripheral blood and total lymphocytes collected per body weight (Figure 1). This correlation was stronger with the CMNC ($r = 0.732$) than the MNC protocol ($r = 0.696$).

In the four linear mixed-effects regression models associated with each efficiency parameter shown in Table 3, the type of ECP protocol was only related to CE1 and CE2 efficiency, with lower values for OPTIA MNC versus OPTIA CMNC, namely −21.98 (95% CI −26.22 to −17.75 in CE1) and −24.12 (95% CI −29.38 to −18.86 in CE2). These models were adjusted for demographic and clinical variables as can be seen in the table, where only the coefficients of those variables that were significant in the different models are shown.

TABLE 3 Performance parameters adjusted according to ECP protocol, patient demographic variables, apheresis parameters and results of blood tests

Variable	CE1	CE2	Haematocrit loss	Platelet loss
Type of ECP protocol				
Optia CMNC	Ref	Ref	Ref	Ref
Optia MNC	−21.98 (−26.22 to −17.75)	−24.12 (−29.38 to −18.86)	ns	ns
Patient demographics				
Gender	ns	ns	ns	ns
Age (years)	ns	0.89 (0.41–1.38)	ns	ns
Weight (kg)	ns	ns	0.00039 (0.0001–0.0006)	ns
Blood results PRE-collection				
Haematocrit (%)	0.56 (0.12–1.00)	ns	0.99 (0.99–1.00)	ns
Leukocytes ($\times 10^6$/ml)	ns	ns	ns	ns
Lymphocytes ($\times 10^6$/ml)	−0.003 (−0.005 to −0.0012)	−0.010 (−0.014 to −0.006)	ns	0.002 (0.0006–0.0046)
Platelets ($\times 10^6$/ml)	ns	ns	ns	0.52 (0.48–0.56)
Apheresis parameters				
TBV processed (fold)	0.001 (0.0007–0.0028)	ns	−2.43e-6 (−4.17e-6 to −6.99e-6)	0.0009 (0.0001–0.0018)
Time (min)	ns	ns	−0.00007 (−0.001 to −7.3e-7)	0.07 (0.01–0.13)
Blood results POST-collection				
Haematocrit (%)	ns	0.72 (0.16–1.28)	−0.99 (−1.00 to −0.99)	1.09 (0.66–1.52)
Leukocytes ($\times 10^6$/ml)	ns	ns	ns	ns
Lymphocytes ($\times 10^6$/ml)	ns	0.006 (0.0014–0.0117)	ns	ns
Platelets ($\times 10^6$/ml)	ns	ns	ns	−0.68 (−0.74 to −0.62)

CMNC Spectra Optia versus COBE Spectra systems

To compare whether the most optimal current procedure is better than the former system, we compared the results obtained using the CMNC system ($n = 374$) and the COBE Spectra device ($n = 868$). Pre-leukocytapheresis characteristics were similar between both groups (Table S1).

The CMNC Optia system showed better results than the COBE Spectra device, including a higher number of leukocytes and lymphocytes collected (Table S2). Collection efficiency parameters (CE1 and CE2) were also better in those procedures performed with the Optia device, $p < 0.001$ (Table S2). The CMNC Optia protocol collects a final product with more volume and lower haematocrit loss. In addition, the loss of platelets was lesser with this procedure (Table 2).

Clinical characteristics and response

Ninety-one patients diagnosed with acute or chronic GvHD were included from September 2006 to November 2019. Clinical characteristics of patients and their donors are reported in Tables 4 and 5. The median number of procedures per patient was 11 (6–17), and 10 patients had 2 different ECP treatment courses.

In total, 71% of patients had either partial ($N = 40$) or complete ($N = 31$) response to treatment (Table 6). Clinical response was not related to the total number of leukocytes or lymphocytes infused, though an association was found between the median number of leukocytes and lymphocytes per infusion (Table 7).

We found no significant changes in the blood cell populations studied except for an increase in the total number of B lymphocytes in those patients who responded to treatment compared with those in whom there was no response (Table S3).

In the multivariate model (Table 8) we observed that response to ECP was associated with a greater post-treatment increase in the total number of B lymphocytes compared with pre-treatment levels (OR = 1.03, 95% CI: 1.00–1.05). Younger age was also associated with a better response (OR = 0.51, 95% CI: 0.29–0.88). The model was validated using a p value associated with the Hosmer–Lemeshow contrast of 0.929 and a c-statistic of 0.893, which indicates that it is a well-calibrated model that correctly classifies 89.3% of the outcomes in patients.

TABLE 4 Patient characteristics ($n = 91$)

Age (years)	
Mean ± standard deviation	10.07 ± 5.63
Weight (kg)	
Mean ± standard deviation	35.86 ± 20.25
Sex *n* (%)	
Male	44 (48.3)
Female	47 (51.65)
Diagnosis	
Haematologic	84 (92.31)
Oncologic	7 (7.69)
Conditioning regimen	
Myeloablative	60 (65.93)
RIC	31 (34.07)
Patient status at transplant	
1 CR	26 (28.57)
2 CR	20 (21.98)
>2 CR	6 (6.59)
PR	4 (4.40)
SD	6 (6.59)
Rel/Ref	7 (7.69)
NE	22 (24.18)

Abbreviations: CR, complete remission; NE, not evaluable; PR, partial response; Ref, refractory; Rel, relapse; RIC, reduced intensity conditioning; SD, stable disease; SD, standard deviation;

TABLE 5 Donor characteristics ($n = 91$)

Stem cell source	*n* (%)
PB	73 (80.22)
BM	7 (7.69)
CB	11 (12.09)
Manipulation	
No	18 (19.78)
Yes	73 (80.22)
Type of donor	
Matched related	23 (25.27)
Haploidentical	38 (41.76)
Matched unrelated	16 (17.58)
Mismatched unrelated	14 (15.38)

Abbreviations: BM, bone marrow; CB, cord blood; HLA, human leukocyte antigen; PB, peripheral blood.

DISCUSSION

There is scant information on ECP procedures in children [2, 4] and reports on lymphocyte collection for these procedures are even more scarce. We believe that such information not only furthers knowledge on procedure safety but also can provide useful background data on lymphocyte collection for chimeric antigen receptor T cell (CAR-T) manufacturing procedures. Therefore, we designed this study not only to analyse the safety and efficacy of our series but also to improve the efficiency of our lymphocyte collection methods for ECP and beyond.

TABLE 6 GvHD features and response to ECP

Variable	N (%)
GvHD	
Acute	50 (54.95)
Chronic	9 (9.89)
Late acute	3 (3.30)
Acute and chronic	29 (31.87)
Response (PR or CR)	
No	20 (21.98)
Yes	71 (78.02)

Abbreviations: CR, complete remission; PR, partial response.

In our study, the most frequent adverse events were those related to the catheter, as reported elsewhere [2, 4, 15]. In the literature, the most common complication related to access was infection (0%–42%) followed by abnormal clotting [4]. In our series, the most frequent adverse event was minor, involving a need to change return/access; other authors may not have considered this to constitute an adverse event. Catheter infection was quite frequent, contrasting with previously published data from our group on stem cell donors [16]. However, it is important to point out that most catheters were used in the context of transplantation and for longer periods of time than those involved in progenitor cell collection. In the literature, citrate toxicity was another important issue, inducing symptoms such as paraesthesia, nausea and vomiting in about 4% of procedures [2], which is a similar rate to that found here. Other adverse events in our series were mild and did not preclude collection completion in most cases. Only one procedure needed to be interrupted, most likely secondary to a severe infection with sepsis.

To the best of our knowledge, this is the largest series in paediatric patients comparing the CMNC and MNC Optia protocols for mononuclear collection. This comparison has been performed previously by other groups in adults undergoing ECP, as in the case of Fante et al., who, as in our study, reported higher CE with the CMNC program (58.7% vs. 42.1%; $p < 0.001$). The authors reported that the MNC program was associated with higher lymphocyte concentration in the final product [17], as found in our series. Putensen et al. also compared CMNC and MNC for T cell collection in adults [18]; however, they observed similar efficiency (CE2%) between CMNC (54.7%) compared with MNC (50.4%).

Regarding haematologic parameters, lymphocyte collections decrease haemoglobin, platelet counts and white blood cells. Thus, a device and protocol that causes less platelet and haematocrit loss will be essential in reducing adverse effects, especially in children. Additionally, higher efficiency of lymph collection is also important, although it remains unclear whether the number of lymphocytes infused influences the response.

On univariate analysis, we found that the Optia blood cell separator used with the CMNC program is more efficient than the MNC

TABLE 7 Relationship between infused cells and response[a]

	All patients ($n = 91$)	Non-responders ($n = 20$)	Responders ($n = 71$)	p value
Total leukocytes infused ($\times 10^6$)	955.63 (521.53–1933.71)	621.68 (376.44–1527.5)	963.49 (577.75–2071.09)	0.269
Total lymphocytes infused ($\times 10^6$/kg)	321.31 (144–887.1)	218.13 (110.23–479.42)	348.7 (164.13–932.25)	0.159
Median leukocytes infused per ECP procedure ($\times 10^6$/kg)	88.38 (51.45–129.07)	63.63 (31.32–11.56)	91.3 (66.14–130.64)	**0.041**
Median lymphocytes infused per ECP procedure ($\times 10^6$/kg)	29.58 (16.98–56.03)	16.98 (8.27–36.73)	34.09 (19.29–56.87)	**0.015**

Note: *P* values <0.05 were considered significant.
[a]Data are reported as median and interquartile range.

TABLE 8 Prediction model for response using a binomial logistic model

	Odds ratio	95% confidence interval	
B lymphocytes (post-pre)	1.03	1.0	1.05
Age (years)	0.51	0.29	0.88
p value (Hosmer–Lemeshow)	0.929		
c-statistics	0.893		

program and causes less platelet loss. A multivariate analysis revealed that the type of protocol only influenced the collection efficiency (CE1 and CE2) when adjusting for other factors; however, it shows no relationship with haematocrit or platelet loss. The Optia CMNC protocol is also more efficient than the formerly used COBE Spectra, as reported in other studies [19].

In our series, clinical response was similar to that reported in previous research [2]. However, it is important to mention the challenge posed by this analysis, because many patients had overlapping features of GvHD (acute and chronic), and in most cases were treated with additional drugs for GvHD.

The univariate analysis showed that clinical response was not related to the total number of cells infused, but rather to the median number of lymphocytes per infusion, thus coinciding with previous studies [20–22]. However, this finding is controversial [23, 24].

Moreover, in the multivariate model, only two variables were associated with a better response to ECP: younger patient age and a greater increase of B lymphocytes after treatment.

Although other studies have reported different findings in cell populations after treatment [3, 25, 26], we found no significant changes after treatment except for an increase in B lymphocytes among ECP responders. This finding is likely related to discontinuation of other concomitant medications for GvHD. Other studies have also pointed to B-cell homeostasis with GvHD as a predictor of response to ECP [27]; however, prospective studies must be conducted to analyse the role of B-cell subsets in ECP treatment.

In conclusion, ECP collection is safe and well-tolerated in most children. Adverse events are mainly related to vascular access problems, and these events are usually mild but more frequent than in progenitor cell collections [16].

This is the first ECP series to compare CMNC versus MNC in a paediatric population. We find CMNC to be the optimal protocol for lymphocyte collection in children. These results could form the basis for research into the use of this software in paediatric lymphapheresis for CAR-T therapy. It is therefore important to conduct prospective studies or clinical trials that include paediatric patients; however, we are aware of the difficulties of doing this and are cognizant of the fact that there are new treatments that, in some cases, are displacing ECP. However, photopheresis remains an effective and safe therapy in children, with few adverse effects, and should continue to be an option in paediatric patients with refractory GvHD. The choice of optimal equipment is essential to improve the efficacy and safety of the procedure in our paediatric patients.

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CONFLICT OF INTEREST

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ORCID

Elena Sebastián https://orcid.org/0000-0002-5444-8076
Miguel Ángel Díaz https://orcid.org/0000-0001-5286-1329

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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SHORT REPORT

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COVID-19 infection and complications according to ABO blood group in the elderly: A population-based subcohort and meta-analysis

Leire Leache[1,2] | Marta Gutiérrez-Valencia[1,2] | Mónica Enguita-Germán[2,3,4,5,6] | Julián Librero[2,3,4,5,6] | Javier Gorricho[7] | Carlos Jericó[8] | Jose Antonio García-Erce[9,10,11]

[1]Unit of Innovation and Organization, Navarre Health Service, Pamplona, Spain

[2]Navarra Institute for Health Research (IdiSNA), Pamplona, Spain

[3]Unit of Methodology, Navarrabiomed, Pamplona, Spain

[4]University Hospital of Navarra (HUN), Pamplona, Spain

[5]Public University of Navarre (UPNA), Pamplona, Spain

[6]Red de Investigación en Cronicidad, Atención Primaria y Promoción de la Salud (RICAPPS), Madrid, Spain

[7]Service of Evaluation and Dissemination of Results, Navarre Health Service, Pamplona, Spain

[8]Department of Internal Medicine, Hospital Sant Joan Despí-Moisès Broggi, Consorci Sanitari Integral, Barcelona, Spain

[9]Blood and Tissue Bank of Navarre, Navarre Health Service, Pamplona, Spain

[10]Grupo Español de Rehabilitación Multimodal (GERM), Aragon Health Sciences Institute (IACS), Zaragoza, Spain

[11]PBM Group, Hospital La Paz Institute for Health Research (IdiPAZ), Madrid, Spain

Correspondence
Jose Antonio García-Erce, Blood and Tissue Bank of Navarre, Calle Irunlarrea 3. 31003, Pamplona, Spain.
Email: jgarcier@navarra.es

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Abstract

Background and Objectives: It is reported that ABO antibodies have a role in COVID-19 infection and severity; however, ABO antibody titres vary with advanced age. The aim was to analyse the association between ABO blood group and risk of COVID-19 infection and complications in elderly patients, and to contrast this data with findings in the overall adult population.

Materials and Methods: A prospective cohort study of the Navarre (Spain) population aged ≥60 years and a meta-analysis of published studies including participants of ≥60 years were carried out.

Results: In the Navarre elderly population, a higher risk of COVID-19 infection was identified in the A versus non-A and O group and lower risk in O versus non-O, with no significant association between hospitalization, intensive care unit admission or mortality and any of the blood groups, results that coincide with those of the overall Navarre adult population. The meta-analyses using studies that included participants of ≥60 years demonstrated a higher risk of hospitalization and mortality in A versus non-A and a lower mortality risk with B versus non-B. Similar mortality results were found in the meta-analyses of the overall adult population.

Marta Gutiérrez-Valencia and Leire Leache contributed equally to this work.

Conclusion: There are no relevant differences between the overall adult population and population aged ≥60 years in the risk of COVID-19 infection and severity according to ABO blood groups, suggesting that age-related changes in ABO would be of limited clinical significance.

Keywords

ABO, blood groups, cohort, COVID-19, meta-analysis

Highlights

- A higher risk of COVID-19 infection was identified in the Navarre, Spain, elderly population with blood group A and lower risk with blood group O.
- There were no significant differences between blood groups in hospitalization, intensive care unit admission or mortality in the Navarre elderly population.
- No relevant differences were found between adults of any age and the elderly population in the risk of COVID-19 infection or severity according to the ABO blood group, suggesting that age-related changes in ABO would be of limited clinical significance.

INTRODUCTION

The COVID-19 infection presents with a considerable spectrum of severity, and host factors may have an impact [1]. As for genetic factors, it has been proposed that anti-A and B antibodies serve as viral neutralizing antibodies for SARS-CoV-2, which could explain in part the differences in risk of infection and complications between ABO groups [2]. However, antibody titres may vary with increasing age, and the clinical significance of these changes is unknown [3–5].

Therefore, the aim was to determine the association between the ABO blood group and the risk of COVID-19 infection and complications (hospitalization, admission to intensive care unit [ICU] and mortality) in elderly patients and to analyse whether these findings differ from those observed in the adult population of any age.

MATERIALS AND METHODS

Two approaches have been used to address the objectives: (1) a cohort study in Navarre (Spain) population aged ≥60 years and (2) a meta-analysis of studies including participants of this age range. This strategy allowed us to contrast the results generated locally with the

TABLE 1 Baseline sociodemographic and clinical characteristics of the cohort of Navarre population of ≥60 years by ABO blood group[a]

Variable	O	A	AB	B	Total	*p* value
N (%)	20,530 (47.9)	18,602 (43.4)	1061 (2.5)	2697 (6.3)	42,890	—
Age, mean (SD)	75.1 (9.6)	75.1 (9.5)	74.7 (9.5)	74.6 (9.3)	75.1 (9.6)	**0.045**
Males, *n* (%)	10,994 (53.6)	9973 (53.6)	554 (52.2)	1418 (52.6)	22,939 (53.5)	0.628
Inmigrants, *n* (%)	519 (2.5)	379 (2.0)	41 (3.9)	128 (4.7)	1067 (2.5)	**<0.001**
Nursing home, *n* (%)	991 (4.8)	845 (4.5)	37 (3.5)	127 (4.7)	2000 (4.7)	0.160
Dependency, *n* (%)	2331 (11.4)	2138 (11.5)	123 (11.6)	290 (10.8)	4882 (11.4)	0.717
Cohabitants, mean (SD)	2.7 (1.7)	2.7 (1.7)	2.6 (1.6)	2.7 (1.7)	2.7 (1.7)	0.446
Dementia, *n* (%)	1116 (5.4)	1026 (5.5)	64 (6.0)	144 (5.3)	2350 (5.5)	0.838
Diabetes, *n* (%)	4677 (22.8)	4467 (24.0)	263 (24.8)	670 (24.8)	10,077 (23.5)	**0.006**
Autoimmune disease, *n* (%)	1521 (7.4)	1371 (7.4)	80 (7.5)	196 (7.3)	3168 (7.4)	0.990
CHD, *n* (%)	6203 (30.2)	5824 (31.3)	304 (28.7)	795 (29.5)	13,126 (30.6)	**0.025**
CKD, *n* (%)	3567 (17.4)	3310 (17.8)	182 (17.2)	477 (17.7)	7536 (17.6)	0.720
COPD, *n* (%)	1583 (7.7)	1539 (8.3)	95 (9.0)	227 (8.4)	3444 (8.0)	0.107
Hyperlipidaemia, *n* (%)	11,837 (57.7)	11,494 (61.8)	625 (58.9)	1607 (59.6)	25,563 (59.6)	**<0.001**
Hypertension, *n* (%)	11,866 (57.8)	10,646 (57.2)	605 (57.0)	1541 (57.1)	24,658 (57.5)	0.672
Stroke, *n* (%)	1985 (9.7)	1856 (10.0)	102 (9.6)	253 (9.4)	4196 (9.8)	0.653
Obesity, *n* (%)	6133 (29.9)	5548 (29.8)	338 (31.9)	849 (31.5)	12,868 (30.0)	0.173
Vaccinated against flu in 2019, *n* (%)	13,490 (65.7)	12,325 (66.3)	696 (65.6)	1759 (65.2)	28,270 (65.9)	0.577

Abbreviations: CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; *N*, number of subjects; SD, standard deviation.

[a]Statistically significant differences are indicated in bold type.

findings from previous evidence generated both at the national and international levels.

Population-based cohort study in Navarre (Spain)

A prospective cohort of the Navarre population ≥18 years with no previous SARS-CoV-2 infection and with known blood group was established in May 2020, and followed up until May 2021, the findings of which have been published elsewhere [6]. For this study, the subcohort of people ≥60 years was selected.

Data for the study were obtained from the BARDENA (Results Analysis Database of Navarre) database, which includes 97% of the Navarre population, and from the Blood and Tissue Bank of Navarre.

The risk of SARS-CoV-2 infection (established by a polymerase chain reaction [PCR]-positive test) was analysed in the whole study population, and the risk of complications in those who were infected. Parametric or non-parametric methods were used to compare continuous variables among blood groups and the chi-square test for categorical variables. Results adjusted by baseline characteristics were estimated using multivariate logistic regression models.

The study protocol was approved by the Ethical Committee for Clinical Research of Navarra (PI_2021/136), which waived the requirement for participant consent.

Systematic review and meta-analysis

On the basis of a previously published systematic review that analysed the risk of COVID-19 infection and severity in adults ≥18 years according to ABO blood groups [7], we selected the individual studies whose population had a mean/median age of ≥60 years or if ≥50% of the population was ≥60 years old.

The meta-analyses of each of the analysed outcome variables (COVID-19 infection, hospitalization, admission to ICU and mortality) were performed based on the identified studies that provided data for the corresponding variable and blood group comparison. The Mantel–Haenszel method and a random-effects model were used. Heterogeneity was analysed using I^2 statistic test, and in cases of substantial heterogeneity ($I^2 > 65\%$), sensitivity analyses were carried out restricting to low risk of bias studies. The risk of bias was analysed using the Newcastle-Ottawa Scale [8].

RESULTS

Results of the population-based cohort study of the Navarre population aged ≥60 years

The cohort included 42,890 people ≥60 years, with a mean age of 75 years. Table 1 shows the baseline characteristics. Results for the association between ABO blood groups and COVID-19 infection and severity are presented in Table 2. A significantly higher risk of

TABLE 2 Association between ABO blood group and risk of COVID-19 infection and severity in the Navarre population of ≥60 years[a]

	COVID-19 infection		Hospitalization		Admission to ICU		Mortality	
	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)
A versus O	**1.11 (1.02–1.20)**	**1.12 (1.03–1.21)**	1.04 (0.87–1.23)	1.04 (0.86–1.24)	0.97 (0.59–1.60)	0.98 (0.59–1.64)	0.98 (0.78–1.23)	0.93 (0.73–1.20)
B versus O	1.09 (0.93–1.28)	1.07 (0.91–1.26)	1.18 (0.84–1.65)	1.14 (0.80–1.62)	1.56 (0.68–3.59)	1.71 (0.73–4.00)	0.95 (0.60–1.51)	0.80 (0.48–1.31)
AB versus O	**0.69 (0.51–0.93)**	**0.70 (0.52–0.94)**	0.67 (0.32–1.39)	0.58 (0.27–1.25)	1.74 (0.41–7.51)	2.00 (0.45–8.87)	0.59 (0.21–1.66)	0.43 (0.14–1.31)
O versus non-O	**0.92 (0.85–0.99)**	**0.92 (0.85–0.99)**	0.96 (0.81–1.14)	0.97 (0.81–1.16)	0.94 (0.59–1.50)	0.91 (0.56–1.47)	1.03 (0.83–1.29)	1.12 (0.88–1.42)
A versus non-A	**1.11 (1.03–1.20)**	**1.12 (1.04–1.21)**	1.03 (0.87–1.21)	1.03 (0.87–1.23)	0.89 (0.56–1.43)	0.89 (0.55–1.44)	1.00 (0.81–1.25)	0.98 (0.77–1.25)
B versus non-B	1.04 (0.89–1.22)	1.03 (0.88–1.20)	1.16 (0.84–1.62)	1.13 (0.80–1.59)	1.56 (0.71–3.46)	1.70 (0.76–3.81)	0.97 (0.62–1.51)	0.84 (0.51–1.36)

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; ICU, intensive care unit; OR, odds ratio.
[a]Statistically significant differences are indicated in bold type.

TABLE 3 Results of the meta-analysis of studies, including population of ≥60 years[a]

	COVID-19 infection		Hospitalization		Admission to ICU		Mortality	
	Studies (*N*)	OR (95% CI); I^2	Studies (*N*)	OR (95% CI); I^2	Studies (*N*)	OR (95% CI); I^2	Studies (*N*)	OR (95% CI); I^2
A versus O	3 (3776)	1.87 (0.81–4.36); 78%	3 (7579)	1.03 (0.76–1.40); 62%	5 (1147)	1.28 (0.98–1.67); 0%	6 (4660)	**1.20 (1.04–1.37)**; 0%
B versus O	3 (3349)	0.98 (0.72–1.33); 0%	3 (4489)	0.94 (0.80–1.10); 0%	5 (686)	1.45 (0.59–3.54); 69%	6 (3764)	0.89 (0.74–1.07); 0%
AB versus O	3 (2391)	1.12 (0.71–1.78); 0%	3 (3916)	**0.75 (0.58–0.97)**; 0%	5 (620)	0.96 (0.50–1.83); 0%	6 (3045)	1.06 (0.77–1.45); 0%
O versus non-O	3 (5528)	0.67 (0.35–1.28); 68%	3 (8560)	1.01 (0.92–1.12); 0%	6 (1634)	0.85 (0.68–1.07); 0%	6 (5865)	0.93 (0.82–1.05); 0%
A versus non-A	3 (5528)	2.00 (0.84–4.77); 84%	3 (8866)	1.13 (0.78–1.61); 75%	5 (1317)	1.19 (0.82–1.71); 37%	7 (5887)	**1.23 (1.08–1.40)**; 0%
B versus non-B	3 (5528)	0.92 (0.71–1.21); 0%	3 (8866)	0.99 (0.85–1.16); 0%	5 (170)	0.98 (0.46–2.11); 0%	6 (5865)	**0.83 (0.70–0.99)**; 0%

Abbreviations: CI, confidence interval; ICU, intensive care unit; *N*, number of participants; OR, odds ratio.
[a]Statistically significant differences are indicated in bold type.

COVID-19 infection was found for the blood group A compared to O (adjusted odds ratio [OR] 1.12, 95% CI 1.03–1.21), also when compared to non-A (adjusted OR 1.12, 95% CI 1.04–1.21) (Table 2). In contrast, people in the blood group AB showed lower infection risk compared to O (adjusted OR 0.70, 95% CI 0.52–0.94) (Table 2). Also, a slightly lower risk was found for the blood group O when compared to non-O (adjusted OR 0.92, 95% CI 0.85–0.99) (Table 2). There were no significant differences between blood groups in hospitalization, admission to ICU or mortality (Table 2).

Results of the systematic review and meta-analysis

Thirteen studies were identified that met the age criteria (Table S1). Table S2 shows the risk of bias assessment of the included studies. The studies included in the meta-analysis of each of the outcome variables are shown in Table S3, and meta-analysis results for COVID-19 infection and severity are presented in Table 3. No significant association was found between any of the blood groups and COVID-19 infection (Table 3). AB group showed a lower hospitalization risk as compared to O (OR 0.75, 95% CI 0.58–0.97, I^2 0%) (Table 3), and sensitivity analyses yielded a higher hospitalization risk with A versus non-A (OR 1.38, 95% CI 1.04–1.83, I^2 0%) (Table S4). No significant differences were identified in the risk of ICU admission between blood groups (Table 3). Blood group A was associated with a significantly higher mortality risk when compared to O (OR 1.20 95% CI 1.04–1.37, I^2 0%) and non-A (OR 1.23, 95% CI 1.08–1.40, I^2 0%), and a lower risk was found for the blood group B when compared to non-B (OR 0.83, 95% CI 0.70–0.99, I^2 0%) (Table 3). In the study by Apea et al., which provided aggregate data that could not be included in the meta-analysis, showed a significantly lower mortality risk in B group as compared to O (adjusted hazard ratio 0.66, 95% CI 0.47–0.92) [9].

DISCUSSION

To date, the association between ABO blood group and susceptibility to COVID-19 infection and severity in people of advanced age has not yet been specifically addressed, and to our knowledge, this cohort study and meta-analysis are the first to provide evidence on this issue.

Regarding the risk of COVID-19 infection, previously published results from the meta-analyses and from the cohort of Navarre adult population of any age [6, 7] coincide in general terms with those obtained in the subcohort of Navarre population ≥60 years, showing a higher risk of COVID-19 infection with A group and lower risk O. By contrast, the meta-analyses of studies in population aged ≥60 years did not find significant differences in risk of infection with any of the blood groups. These discrepancies between the findings from the cohort study and the results from the meta-analyses may be due to the fact that two of the three studies used to meta-analyse this outcome (which sums up at least 84% of the sample) were conducted in Iran, suggesting a possible contribution of other potential social,

racial and demographic confounding factors, and of differences in COVID-19 detection capacity and prevention measures.

As for hospitalization risk, findings from the cohort and the meta-analyses in the overall adult population [6, 7] were almost maintained when limited to people of advanced age, not showing any significant association according to blood groups, except for AB, in which a lower hospitalization risk was identified in the meta-analysis. Also, when restricted to studies with a low risk of bias, the A group showed a higher hospitalization risk when compared to non-A.

No significant differences were identified in the risk of ICU admission between blood groups in the subcohort of people of ≥60 years or in the meta-analyses, results that coincide with those obtained from the overall adult population [6, 7]. Meta-analyses showed a higher mortality risk in people of advanced age with A versus non-A blood groups, and a lower risk with B versus non-B, observations that were already reported in the meta-analyses of adult population of any age [7].

Although an effect of immunosenescence on agglutinin protection cannot be ruled out, our findings, in general, did not suggest differences with respect to the adult population of any age in the risk of COVID-19 infection and severity according to the ABO blood group. This may support the hypothesis that the significance in real clinical practice of the age-related changes in A and B antibody titres and protection would be of questionable magnitude [5] and may also point out that other mechanisms apart from the role of antibodies may be involved on the variability in risk of COVID-19 according to blood group.

Our cohort study can be considered representative of the Navarre population aged ≥60 years, as it included almost the entire population of this age. Also, the validation process to which the BARDENA database is subjected ensures the quality of the information. Moreover, the results were adjusted by several possible confounding factors, which enhances the robustness of the findings. On the other hand, the meta-analyses carried out enables us to contrast the concordance of results of our cohort study with those from other national and international studies. A rigorous methodology was applied, and the review process was carried out independently by two reviewers, which guarantees their validity.

In conclusion, a higher risk of COVID-19 infection was identified in the Navarre elderly population with A versus non-A and O blood group and a lower risk in O versus non-O, findings that were already observed in the overall adult population [6]. Although no significant differences in severity were identified between blood groups in the Navarre elderly population, meta-analyses results demonstrated a higher risk of hospitalization and mortality in A versus non-A, and lower mortality risk with B versus non-B. Similar results for mortality were found in the meta-analyses of the overall adult population [7]. In general terms, we identify no relevant differences in the risk of COVID-19 infection and severity according to the ABO blood group between the overall adult population and population aged ≥60 years. However, future studies should analyse this relevant matter in greater depth.

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L.L was involved in conceptualization of the study. L.L., M.G.-V., M.E.-G. and J.L. were involved in developing the methodology for the study. L.L., M.G.-V., M.E.-G. and J.L. were involved in formal analysis and software. L.L. and M.G.-V. wrote the original draft. L.L., M.G.-V., M.E.-G., J.L., J.G., C.J. and J.A.G.-E were involved in draft review and editing.

CONFLICT OF INTEREST

The authors declare no conflict of interest for this study.

ORCID

Leire Leache https://orcid.org/0000-0003-2272-7086
Marta Gutiérrez-Valencia https://orcid.org/0000-0002-3229-6614
Mónica Enguita-Germán https://orcid.org/0000-0002-2890-1252
Julián Librero https://orcid.org/0000-0002-4859-9054
Javier Gorricho https://orcid.org/0000-0003-3609-9922
Carlos Jericó https://orcid.org/0000-0003-1049-4027
Jose Antonio García-Erce https://orcid.org/0000-0001-7662-6286

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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SHORT REPORT

Vox Sanguinis ISBT International Society of Blood Transfusion

Genetic background of anti-Xg^a producers in Japanese blood donors

Naoko Watanabe-Okochi[1] | Makoto Uchikawa[1] | Hatsue Tsuneyama[1,2] | Kenichi Ogasawara[2] | Risako Shiraishi[2] | Atsuko Masuno[1] | Takayuki Onodera[1] | Nelson-Hirokazu Tsuno[1] | Kazuo Muroi[1]

[1]Kanto-Koshinetsu Block Blood Center, Japanese Red Cross Society, Tokyo, Japan

[2]Central Blood Institute, Japanese Red Cross Society, Tokyo, Japan

Correspondence
Naoko Watanabe-Okochi, Kanto-Koshinetsu Block Blood Center, Japanese Red Cross Society, 2-1-67, Tatsumi, Koto-ku, Tokyo 135-8639, Japan.
Email: n-okochi@ktks.bbc.jrc.or.jp

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Abstract

Background and Objectives: The Xg blood group is composed of two antigens, Xg^a (XG1) and CD99 (XG2 and MIC2). The *XG* and *CD99* are homologous genes located on pseudoautosomal region 1 of the X and Y chromosomes. The expressions of Xg^a and CD99 are co-regulated by a single nucleotide polymorphism (rs311103) in the GATA-1 binding region. Another mechanism of the Xg(a−) phenotype is the genomic deletion of approximately 114 kb, including the *XG* gene. Anti-Xg^a seems to be naturally occurring by detection in males who have never been transfused.

Materials and Methods: In this study, we identified 23 anti-Xg^a producers among 580,115 donors (0.004%). Additional 12 anti-Xg^a producers were also identified from a separate cohort.

Results: All 35 anti-Xg^a producers were male. Genomic DNA was obtained from 34 of 35 producers, and all 34 producers were confirmed to carry the *XG*-gene-deficient allele (*XGdel*). The breakpoints of all 34 producers were identical. The *XGdel* was also identified in 12 non-producers of anti-Xg^a among 860 donors who have no antibodies against RBCs, and the breakpoints were also identical with the anti-Xg^a producers.

Conclusion: Our results will serve as the basis for a more complete understanding of Xg blood group polymorphisms.

Keywords

anti-Xg^a, esv2662319, rs311103, *XG* deficient

Highlights

- The frequency of the anti-Xg^a producers in Japanese blood donors was 0.004% (23/580,115).
- All anti-Xg^a producers were males and had the *XG*-deficient allele. Interestingly, the *XG*-deficient allele was also identified in male non-producers of anti-Xg^a.
- The frequency of Xg_{null} in males with rs311103GG is not so rare (4 of 244, 1.64%), but anti-Xg^a producer is rare (23 of 359,341, 0.0064%).

INTRODUCTION

The Xg blood group is composed of two antigens, Xg^a (XG1) and CD99 (XG2 and MIC2). In 1962, anti-Xg^a was identified in a male patient who received frequent blood transfusions [1]. Family studies revealed that the Xg^a antigen was encoded by a gene linked to the X chromosome. The *XG* gene was cloned from the pseudoautosomal boundary region in 1994 [2]. The XG glycoprotein is presumed to be a type I membrane protein consisting of 180 amino acid residues; however, its function remains unknown.

The frequency of Xg(a−) in the Japanese population is 30.6% in males and 11.2% in females [3]. Most anti-Xg^a producers are males who have never been transfused; thus, anti-Xg^a seems to be a naturally occurring antibody that does not cause haemolytic transfusion reactions [3–5]. Notably, only one case of anti-Xg^a was suspected of causing a transfusion reaction [4]. Anti-Xg^a producers are generally in the IgG subclass, which reacts by antiglobulin methods.

XG and *CD99* genes are located on the pseudoautosomal region 1 (PAR1) of the X (Xp22.3) and Y (Yp11.2) chromosomes. *XG* and *CD99* are exempt from the control of X-chromosome inactivation and are inherited in an autosomal dominant manner [6]. The first three exons of the *XG* gene on the X chromosome are situated in PAR1, whereas the other seven exons are in the X-specific region (Figure 1). The *XG* gene on the Y chromosome has only three exons in PAR1, and the XG protein cannot be produced from the Y chromosome [7].

The number of *XG* mRNA in Xg(a−) was considerably lower than that in Xg(a+) [8]. A single nucleotide polymorphism (SNP) in the GATA-1 binding region was related to the regulation of Xg^a expression [9, 10]. The SNP (rs311103) is located 3.7 kb upstream of the transcription start site of the *XG* gene (Figure 1). If rs311103 is 'G', GATA-1 family transcription factors can bind to the regulatory region and Xg^a is expressed. If rs311103 is 'C', GATA-1 cannot bind to the regulatory region and Xg^a is not expressed. The GATA1 regulation affects especially the erythroid cells, but Xg^a could express on other tissues presumably not under GATA1 regulation (https://www.genecards.org/cgi-bin/carddisp.pl?gene=XG). The minor allele frequency of rs311103 G > C is 0.37 in the 1000 Genomes Project, which is a catalogue of common human genetic variation (http://asia.ensembl.org/Homo_sapiens/Variation/Explore?r=X:2747843-2748843;v=rs311103;vdb=variation;vf=698278790).

Another mechanism of the Xg(a−) phenotype is the lack of the *XG* gene on the X chromosome. Lee et al. reported that individuals producing anti-Xg^a had a rare allele of 114 kb deletion (esv2662319), including exon 4 through exon 10 of the *XG* (Figure 1a) [11].

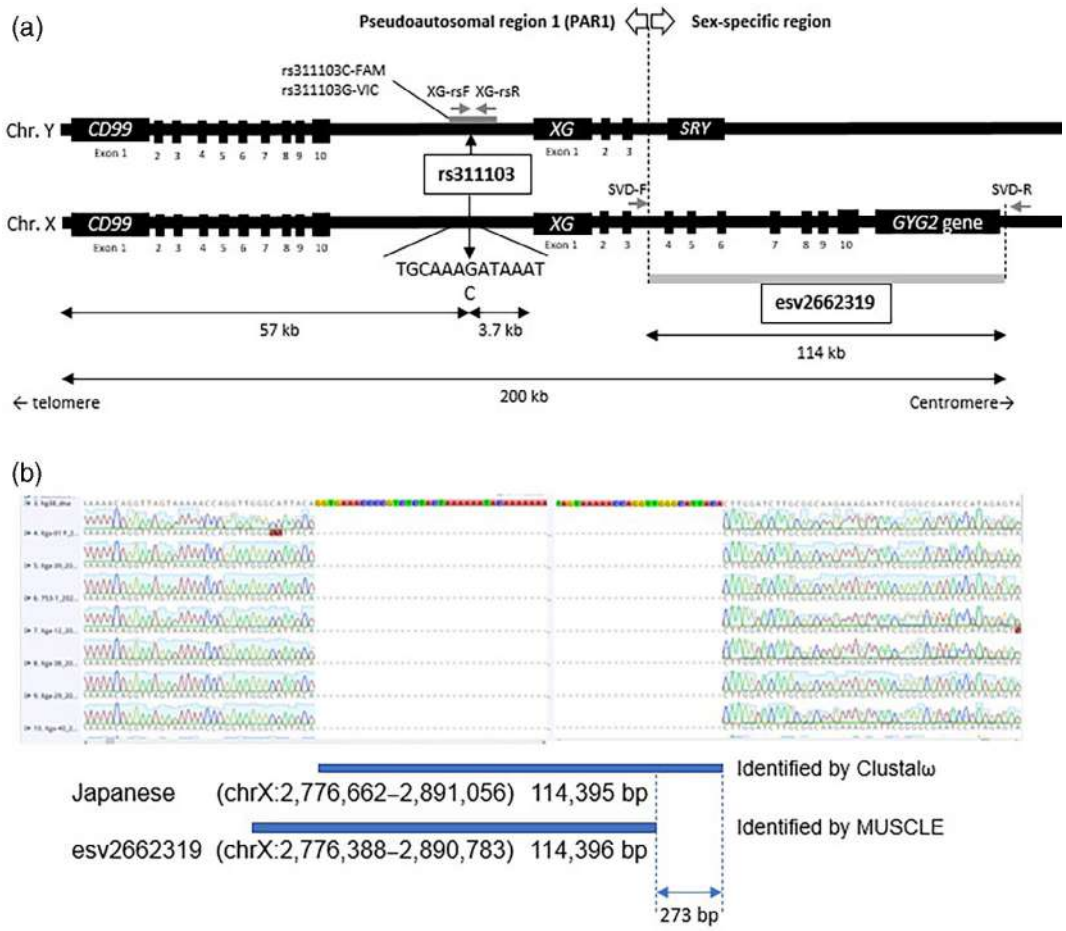

FIGURE 1 (a) Structure of *XG* and *CD99* genes on the X and Y chromosomes. Grey arrows indicate primer positions. Grey bar indicates the TaqMan probe position. (b) Sequence analysis data for the *XGdel* by ClustalW (Geneious). The breakpoint was shifted 273 bp from esv2662319. The shift of the breakpoint observed in our study might be due to the repetitive DNA motif and the ClustalW alignment algorithms.

The Xg$_{null}$ individuals have no Xg^a antigen not only in erythrocytes but also in tissues.

In this study, we investigated the genetic background of anti-Xg^a producers among Japanese blood donors. Additionally, the presence of the *XG*-deficient allele (*XGdel*) in non-producers of anti-Xg^a was assessed.

MATERIALS AND METHODS

Samples

Blood samples of the individuals with anti-Xg^a were screened from 580,115 blood donors (359,341 males and 220,774 females; total of 1,476,301 donations) at the Japanese Red Cross Kanto Koshinetsu Block Blood Center from November 2019 to April 2021. Written informed consent was obtained from all blood donors before blood sampling. Anti-Xg^a in plasma was identified by irregular antibody screening. In addition, 860 blood samples with a determined Xg phenotype, which have no antibodies against RBCs, were used for molecular genetics analysis to identify the *XGdel* among anti-Xg^a non-producers (Table S1). The 860 samples were selected to make RBC panels for antibody identification in our routine work; therefore, it was not a random selection, but we selected them without considering the Xg^a phenotype. This study was approved by the ethics committee of the Japanese Red Cross Society (#2019-038 and #2020-044).

Serology

Standard serological tests were performed for the Xg^a phenotype using an indirect antiglobulin test with a monoclonal anti-Xg^a (HIRO-123, in-house) by the tube method. Anti-Xg^a in plasma was detected by antiglobulin methods using IH-1000 (Bio-Rad Laboratories, Portland, ME).

TaqMan-PCR for rs311103 genotyping

The 10 μl PCR reaction contained 20–40 ng of genomic DNA, 5 μl of TaqPath ProAmp Master Mix (Thermo Fisher Scientific, Tokyo, Japan), and the following primers and TaqMan probes at the indicated concentrations: XG-rsF and XG-rsR primers (0.9 μM), XG-rsC FAM-MGB probe (0.2 μM) for the detection of rs311103C and XG-rsG VIC-MGB probe (0.2 μM) for the detection of rs311103G (Table S2). The PCR condition was 95°C for 30 s followed by 40 cycles of 5 s at 95°C and 30 s at 60°C (StepOne Plus, Applied Biosystems, Tokyo, Japan).

PCR and sequencing for the *XGdel*

Genomic DNA was extracted from peripheral blood leucocytes using a QIAamp DNA Blood Mini Kit (Qiagen, Tokyo, Japan). To detect the *XGdel*, we performed PCR using SVD-F primer specific for *XG* intron 3 and SVD-R primer specific for the downstream region of the breakpoint of the 114-kb deletion (Table S2) [11]. Genomic DNA (20–40 ng) was amplified by 35 cycles of PCR in a 10 μl volume containing PCR buffer with 0.2 units of Phusion DNA polymerase (New England BioLabs, Tokyo, Japan), 0.2 μl of 10 mM dNTPs, 0.3 μl of 99.5% dimethyl sulphoxide (Wako, Osaka, Japan), 0.5 μl of 20 nM SVD-F and 0.5 μl of 20 nM SVD-R under the following conditions: one cycle of 30 s at 98°C and 35 cycles of 10 s at 98°C, 30 s at 64°C and 30 s at 72°C (Veriti, Applied Biosystems, Waltham, MA). Purified PCR products were sequenced with a 3500XL Genetic Analyser (Applied Biosystems) using a BigDye Terminator v1.1 Cycle Sequencing Kit (Applied Biosystems) with the sequencing primer (SVD seq-FW, Table S2). The sequence data were analysed using ClustalW and MUSCLE with Geneious Prime (Geneious, Auckland, New Zealand).

RESULTS

All anti-Xg^a producers among Japanese donors were males and carried the *XGdel*

From November 2019 to April 2021, irregular antibody screenings were performed on 580,115 individuals (359,341 males and 220,774 females), and 23 anti-Xg^a producers (0.004%) were identified. In addition to these individuals, six anti-Xg^a producers were collected outside of the survey period and six more were collected from different regions of Japan (two from the Hokkaido Block Blood Centre and four from the Tohoku Block Blood Center). All 35 anti-Xg^a producers were male, and DNA samples were obtained from 34 of them. We confirmed that all 34 anti-Xg^a producers carried the *XGdel* by the PCR method (Figure 2).

Genetic background of the anti-Xg^a producers

We sequenced the breakpoints in the *XGdel* of the 34 anti-Xg^a producers and confirmed that all were identical (Figure 1b). The deleted length was 114,395 bp, located at chrX:2,776,662–2,891,056 in the 2013 (GRCh38/hg38) Assembly by ClustalW (Geneious). The breakpoint was 273 bp shifted from esv2662319 located at chrX:2,776,388–2,890,783. However, if the same sequence data were analysed by MUSCLE (Geneious), the same breakpoint as esv2662319 was identified. Among the 34 anti-Xg^a producers, 21 were rs311103GG (61.8%), 12 were GC (35.3%) and only one case was CC (2.9%).

The *XGdel* was also identified in non-producers of anti-Xg^a

A total of 860 blood samples from blood donors who had no antibodies against RBCs were analysed for rs311103 genotype by TaqMan-PCR (Table S1). Among the 860 non-producers, 351 were

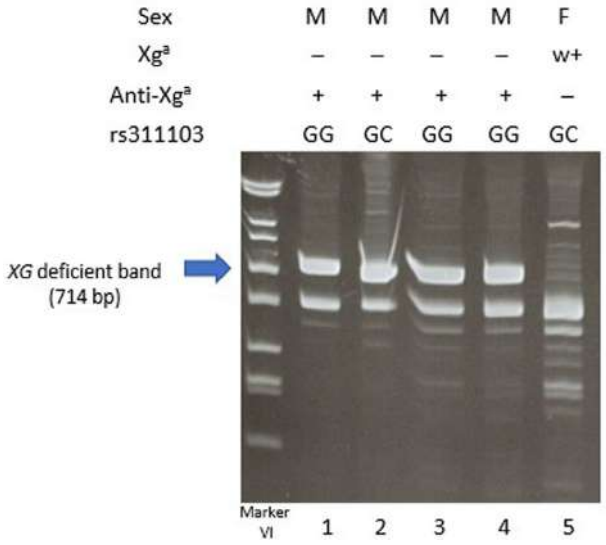

FIGURE 2 PCR for the *XGdel* successfully amplified in anti-Xg^a producers. The 714-bp band indicates the presence of the *XGdel*. The sample of line 5 is a negative control of anti-Xg^a non-producer of a female with weak Xg(a+) phenotype. Marker VI is DNA molecular weight (Roche diagnostics, Mannheim, Germany).

rs311103GG (40.8%), 385 were GC (44.5%) and 126 were CC (14.7%). Four Xg(a−) males with rs311103GG, five Xg(a−) females with rs311103GC and one Xg(a−) female with rs311103GG did not match the phenotype with the rs311103 genotype; therefore, all of them were subjected to the *XG* deficient analysis by PCR. Anti-Xg^a producers had a high frequency of rs311103GG, probably due to the linkage between *XGdel* and rs311103G. Therefore, 106 Xg(a+) females with rs311103GG, 76 Xg(a−) males with rs311103CC and 50 Xg(a−) females with rs311103CC were analysed for the presence of *XGdel*. The *XGdel* was identified in four Xg(a−) males with rs311103GG, five Xg(a−) females with rs311103GC and three Xg(a+) females with rs311103GG. All eight females had exon 8 of the *XG* gene, confirmed by PCR [11], and considered heterozygous for the wild-type *XG* gene. We confirmed that the breakpoints of the *XGdel* in the 12 non-producers were identical to that of the anti-Xg^a producers. One case of Xg(a−) female with GG was not identified as the *XGdel*. We speculated that the record about XG phenotype might be wrong because some females could show very weak expression of Xg^a. Therefore, we tried to take a serological test using a new sample from this donor. The *XGdel* was not identified among the 76 Xg(a−) males and 50 Xg(a−) females with rs311103CC.

DISCUSSION

The frequency of anti-Xg^a among Japanese blood donors was found to be 0.004% (23 in 580,115). All of the anti-Xg^a producers were males and carried the rare *XG* allele lacking exons 4–10. We confirmed that the breakpoint was identical in all analysed samples. The breakpoint appeared to be 273 bp shifted from esv2662319. The PCR product to detect the 114-kb deletion (esv2662319) was 714 bp [11]. There were homologous sequences at the breakpoints, and this deletion generated a repetitive DNA motif LTR6B, of which over 500 copies exist throughout the human genome. The 520-bp core consensus sequence was aligned to the X chromosome surrounding both breakpoints. Lee et al. speculated that the homologous sequences caused the recurrent nature of this recombination event in unrelated individuals.

In this study, all anti-Xg^a producers carried the *XGdel*, and also non-producers of anti-Xg^a carried the same allele. The *XGdel* was identified in 12 individuals among 860 Japanese blood donors. The *XGdel* was identified in the 1000 Genomes data set: 23 in 1092 donors [12]. Four Xg$_{null}$ donors with the *XGdel* were identified among 599 male non-producers of anti-Xg^a. The frequency of Xg$_{null}$ in males with rs311103GG is not so rare (4 of 244, 1.64%), but anti-Xg^a producer in males is rare (23 of 359,341, 0.0064%). There were no Xg$_{null}$ identified among 261 females, because homozygosity for the *XGdel* is quite rare.

Among 860 non-producers, 9 were mistyped as Xg phenotype by the rs311103 genotyping due to the *XGdel* allele. This is approximately 1% error rate that would have occurred if typing was performed only with rs311103 in the Japanese population. Although not all 860 donors were screened, at least 12 of 860 donors carried the *XGdel*, and 3 females among these 12 cases were heterozygous for the *XG* allele, and thus would not be detected as discrepant based on the rs311103 screening.

We anticipate that our present results will serve as the basis for a more complete understanding of Xg blood group polymorphisms. Further studies will be required to clarify the differences between producers and non-producers of anti-Xg^a among Xg$_{null}$ individuals.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

ORCID

Naoko Watanabe-Okochi https://orcid.org/0000-0002-2362-257X
Kenichi Ogasawara https://orcid.org/0000-0001-7675-7227
Nelson-Hirokazu Tsuno https://orcid.org/0000-0002-7619-6500

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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LETTER TO THE EDITOR

Vox Sanguinis ISBT International Society of Blood Transfusion

Gender equity analysis of board of directors for transfusion medicine professional societies around the world

Medical subspecialty societies are paramount to advancing their respective fields, conveying and disseminating research and clinical practice guidelines, and representing, supporting and advocating for society members. Despite these responsibilities, research has demonstrated that significant gender inequities exist among governing committees and committee leadership for numerous medical subspecialty societies [1–3]. We recently highlighted significant gender inequity among blood banking and transfusion medicine (BBTM) society recognition award recipients, with women underrepresented even when considering the number of women practising and performing research in the field [4]. Therefore, we sought to investigate whether similar gender inequities exist among the board of directors (BODs) for BBTM professional societies and if these may contribute to inequities in this field.

We performed a cross-sectional analysis of the BODs of 10 BBTM professional societies as of 31 May 2022 and assessed the gender composition of the BODs and board leadership positions (Table 1). Using previously described and well-established methods [1–5], gender was determined via online review of pronouns. If unavailable, photograph and name were used in combination. Statistical analyses were conducted using GraphPad PRISM version 9.2.0 (GraphPad Software, LLC San Diego, CA, USA), with a p-value <0.05 considered significant.

A total of 125 BOD positions are held by 123 unique individuals. One man and one woman each hold two positions. Women hold significantly more positions compared to men on the 10 societies' BODs (59.2%, 74/125 vs. 40.8%, 51/125; $p = 0.040$). In all, 46 leadership positions are held by 45 individuals (one woman holds two positions), with significantly more leadership positions held by women (71.7%, 33/46 vs. 28.3%, 13/46; $p = 0.003$).

Individually, six societies have more women on their boards, two have an equal number of women and men and two have more men. Gender representation ranges from 100% women (Canadian Society for Transfusion Medicine) to 70% men (Africa Society for Blood Transfusion).

These findings demonstrate that in contrast to other medical subspecialty societies, the BODs for BBTM professional societies do not have significant underrepresentation of women. More women serve on BBTM BODs and outnumber men on 6 of 10 boards. Furthermore, women are significantly more likely to hold board leadership positions. These findings are surprising given our recent study highlighting the significant underrepresentation of women among BBTM society recognition award recipients, potentially suggesting that women work for societies' boards but do not receive recognition in the form of awards. Conversely, this could indicate that the field of BBTM has begun to recognize and is attempting to rectify historical inequities. Regardless, diversity, equity and inclusion advocacy is crucial to ensure progress is

TABLE 1 Gender composition of BBTM professional societies' boards of directors

	Boards of directors overall		Leadership positions[a]	
Society	Women: % (*n*)	Men: % (*n*)	Women: % (*n*)	Men: % (*n*)
International Society of Blood Transfusion	75% (12)	25% (4)	63% (5)	38% (3)
Canadian Society for Transfusion Medicine	100% (10)	0% (0)	100% (5)	0% (0)
British Blood Transfusion Society	50% (5)	50% (5)	50% (3)	50% (3)
Irish Blood Transfusion Service	67% (8)	33% (4)	100% (1)	0% (0)
Northern Ireland Blood Transfusion Service	45% (5)	55% (6)	100% (3)	0% (0)
Australian & New Zealand Society of Blood Transfusion	67% (4)	33% (2)	75% (3)	25% (1)
Africa Society for Blood Transfusion	30% (3)	70% (7)	100% (2)	0% (0)
Association for the Advancement of Blood and Biotherapies	50% (10)	50% (10)	33% (2)	67% (4)
American Society for Apheresis	54% (7)	46% (6)	83% (5)	17% (1)
Society for the Advancement of Patient Blood Management	59% (10)	41% (7)	80% (4)	20% (1)

[a]Chair, executive director, chief executive, president, president-elect, past president, vice president, treasurer and secretary.

sustained and does not encounter setbacks. Further work is needed to promote diversity and equity among society leadership not only with respect to gender but also race, ethnicity, sexual orientation and additional identifying demographics.

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J.W.J. performed the research and wrote the first draft of the manuscript. B.D.A. and G.S.B. supervised the research and reviewed and edited the manuscript.

CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this research.

Jeremy W. Jacobs[1]
Brian D. Adkins[2]
Garrett S. Booth[3]

[1]*Department of Laboratory Medicine, Yale School of Medicine, New Haven, Connecticut, USA*
[2]*Department of Pathology, Division of Transfusion Medicine and Hemostasis, University of Texas Southwestern, Dallas, Texas, USA*
[3]*Department of Pathology, Microbiology and Immunology, Vanderbilt University Medical Center, Nashville, Tennessee, USA*

Correspondence
Jeremy W. Jacobs, Department of Laboratory Medicine, Yale School of Medicine55 Park Street, New Haven, CT 06520, USA.
Email: jeremy.jacobs@yale.edu

ORCID

Jeremy W. Jacobs https://orcid.org/0000-0002-5719-9685
Brian D. Adkins https://orcid.org/0000-0002-9480-2762
Garrett S. Booth https://orcid.org/0000-0002-8422-9480

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ERRATUM

In the published article by Lewin et al. [1] that appeared in volume 116, page 946, the name of the 6th author was incorrectly spelled. This author should have been listed as "Helen Faddy" instead of "Helen Fady".

The author apologizes for the error.

REFERENCE

1. Lewin A, Drews SJ, Lieshout-Krikke R, Erikstrup C, Saeed S, Faddy H, et al. An international comparison of anti-SARS-COV-2 assays used for seroprevalence surveys from blood component providers. Vox Sang. 2021;116:946–54.

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DIARY OF EVENTS

See also https://www.isbtweb.org/events/hvwebinars.html	
18 October 2022	ISBT Corporate Partner Educational Webinar Terumo BCT: Electronic data transfer: a new layer for blood safety
26 October 2022	ISBT Live Journal Club: Six sigma in blood transfusion services: a dream too big in a third world country?
17–21 June 2023	ISBT Gothenburg 2023
18–21 November 2023	ISBT Cape Town 2023

