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Perspective de recherche

How do I/we forecast tomorrows' transfusion: Blood components

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ABSTRACT

The current implementation of Pathogen Reduction Technologies (PRTs) offers advantages and disadvantages to transfusion medicine. PRT rollout may significantly reduce the incidence of transfusion-transmitted infections and immune reactions, while offering a 'one-size-fits-all' solution to future pathogens in blood products. However, the decrease in transfusion efficacy of PRT-treated blood products suggests that the demand for blood products may increase, further straining the already limited supply of these cells. Conversely, cold-stored platelets and whole-blood transfusions have re-emerged, potentially granting more effective transfusion options to bleeding patients. The renewed focus on donor variability, storage quality, and transfusion outcome presents another avenue through which transfusion quality and supply may be improved.

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With the recognition that human immunodeficiency virus (HIV) could be transmitted by blood products in the 1980s, a major focus in transfusion medicine became the improvement of safety with regards to pathogens. Until recently, the primary means of combating transfusion-transmitted infections (TTIs) was the screening of donors for disease, as well as testing the donated product for infectious agents. However, these measures cannot adequately target all pathogens, such as chikungunya, dengue, or *Plasmodium* parasites [1]. Furthermore, this strategy is inherently reactionary, and thus leaves blood banking vulnerable to new pathogens to which we cannot respond to immediately. To address these problems, Pathogen Reduction Technologies (PRTs) were developed to act as a one-stop solution to any transmissible agent that might be present in the transfusion product. The technologies are based on UV-light irradiation, with or without photosensitizer, to destroy nucleic acids, thereby inactivating invaders and preventing their replication. Presently, there are three technologies authorized in Europe, and one in the United States, for use in platelet concentrates. One is the addition of amotosalen and irradiation with UV-A light (INT, INTERCEPT[®] Blood Systems, Cerus Corporation, Concord, USA), licensed in both Europe and the United States. The second is the addition of riboflavin (vitamin B₂) and irradiation with UV-

B light (MIR, Mirasol[®], TerumoBCT, Lakewood, USA). The last uses only UV-C under continuous agitation (TFU, Theraflex UV[®], MacoPharma, Mouvoux, France).

While the risk of TTIs is relatively low with current preventative measures, the incidence of TTI and transfusion reactions is still high for patients who receive numerous platelet products throughout their lives. Bacterial contamination of platelet concentrates, namely with *Staphylococcus* and *Bacillus* genera, is also a persist problem despite our best efforts. Fortunately, PRTs have proven highly efficacious in reducing transfusion-related infections, whether from enveloped and non-enveloped viruses, gram positive- and negative-bacteria, and parasites [2]. Indeed, the FDA approved INTERCEPT as a replacement for testing for Zika virus in 2016 [3]. While no clinical trials have directly assessed the incidence of sepsis or TTI in PRTs, the conclusion is that for their pathogen-reducing properties, PRTs are a valuable tool for ensuring transfusion safety.

Because PRT treatment also destroys white blood cells (WBCs), PRT-PC transfusion also has a lower incidence of adverse immune response. PRT treatment inhibits WBC antigen presentation, cytokine synthesis, and T-cell proliferation [4,5]. Both the SPRINT and EFFIPAP trials found that patients receiving PRT-PC platelets experienced less adverse transfusion reactions than their untreated counterparts [6]. This is compounded by the licensing of platelet additive solutions (PAS), crystalloid nutrient media that can replace plasma for platelet storage [7]. Taken together, the incidence of graft-vs-host disease in blood transfusion is lower than at any time in history.

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PRTs and transfusion quality

An important concern with regards to PRTs is their deleterious effects on platelet quality. UV irradiation is known to damage platelets by destroying their mRNA and miRNA as well as doing non-specific damage to cellular proteins [8]. PRT-treated platelet concentrates (PRT-PCs) display statistically significant increases CD62P exposure, glucose expenditure, and lactate generation, suggesting that the cells are also activated by the treatment [9]. *In vivo*, transfused PRT-PCs demonstrate lower rates of recovery and survival when compared to untreated cells [10].

Several clinical studies comparing INTERCEPT-treated and untreated platelets have been carried out, including the euroSPRITE, SPRINT, EFFIPAP, and TESSI [6,11,12]. These studies, and several meta-analyses of their results, have consistently returned that PRT-PCs are inferior transfusion products. The most consistent finding is that transfusion of INTERCEPT-platelets is associated with a significant decrease in 1 h and 24 h CCI [13,14]. A shortened interval between consecutive platelet transfusions was also found in INTERCEPT- vs untreated platelets [13]. In contrast, there appears to be no statistically significant difference in the frequency of WHO-grade bleeding events between INTERCEPT- and untreated PCs. However, it should be noted that this finding is inconsistent: Depending on which studies are included, and whether expanded safety analysis data is considered instead of the initial reports collected during the studies, increases in clinically significant bleeding with regards to INTERCEPT-treated platelets are indeed found. However, at this time, there is insufficient high-quality evidence to confirm that PRT-PCs leave patients at higher risk of WHO Grade 2 or greater bleeding events.

Pathogen reduction technologies and red blood cells

Pathogen reduction technologies for red blood cells will be an important safety measure as we currently have few options. Cerus has developed a red cell solution, but it is not yet licensed. This process may provide adequate killing of pathogens and provide enhances product safety.

PRTs and platelet storage

Because PRTs are ineffective at high bacterial titres, platelet products must be treated at the point of manufacture to avoid the bacterial load outpacing the capacity of the system. The effects of PRT treatment on platelet storage quality are thus an important consideration for blood banking. UV irradiation is known to damage platelets by destroying their mRNA and miRNA loads as well as doing nonspecific damage to cellular proteins [8]. Platelets treated with PRTs display statistically significant increases CD62P exposure, glucose expenditure, and lactate generation, suggesting that the cells are also activated by the treatment [9]. PRT-treated platelets also undergo accelerated apoptosis due to upregulation of Bak proteins and caspase-3 activation [15], and display increased phosphatidylserine on their surface [15,16]. Collectively, these changes are known to reduce the storage quality of the cells, limiting the shelf-life of the transfusion product. As such, implementation of this technology could increase scarcity of platelet products as demand and wastage both increases. However, making platelets available sooner by removing the bacterial screening period may increase platelet supply [17]. Further, no studies to date have demonstrated that hospitals which use PRT-treated platelets consume more transfusion products on average. That said, the markers linked with poor platelet storage are demonstrably elevated in PRT-treated platelets, and clinical trials have shown that these products produce lower CCIs and require more transfusions

overall. All said, widespread PRT implementation could strain platelet supply, but more data is required to grasp the scope of the problem.

Overview of Platelet-PRT clinical trial results

In the euroSPRITE trial, mean 1-hour posttransfusion platelet corrected count (CCI) in the first 8 transfusions was lower in INTERCEPT-platelet-receiving patients compared to recipients of untreated platelets (27.5 vs 35.8, $P = 0.03$). However, after adjusting for differences in platelet dose using the CCI, there was no statistical difference (13100 vs 14900, $P = 0.11$). In contrast, the mean 24-hour posttransfusion CCI was less for the test group than control, even after adjustment (7400 ± 550 vs 10600 ± 7100). There were no statistical differences in hemostasis, hemorrhagic adverse events, or overall adverse events [11].

The SPRINT trial had primary endpoint of proportion of patients with WHO Grade 2 or higher bleeding during the period of platelet support (non-inferiority threshold 12.5 % for Grade 2, 7 % for Grade 3–4). In the SPRINT trial, the mean 1-hour posttransfusion platelet CCI (11.1×10^3 vs 16.0×10^3 control), average number of days to the next transfusion (1.9 vs 2.4), and number of transfusions needed (8.4 vs 6.2), were all elevated in INTERCEPT-platelet-receiving patients ($P < 0.001$) [6]. However, incidence of World-Health Organization (WHO) Grade 2, 3, and 4 bleeding was not statistically different between PRT-treated and untreated platelets. Transfusion reactions were also lower in the INTERCEPT-platelet group (3.0 % vs 4.4 % control, $P = 0.02$). Re-analysis of the SPRINT data confirmed the equivalency for the prevention of bleeding and the number of transfused PC and RBC units. Acute transfusion reactions within 6 h were also significantly lower compared to reference platelets.

The TESSI study evaluated the efficacy and safety of transfusing INTERCEPT-treated platelet stored for 6–7 days [12]. The primary endpoint was the 1 h CCI with an accepted inferiority of 30 %, with secondary endpoints of 1- and 24-h count increment, 24-h CCI, time to next platelet transfusion, red cell use, bleeding, and adverse events. 1-h CCI was found to be non-inferior ($p = 0.007$) with respect to the mean 1-h CCIs. Posttransfusion bleeding and RBC use were not significantly different. Median time to the next PC transfusion after study PC was not significantly different. The 24 h CCI (2489 vs 6549) and 24-h count increments (11.1 vs $15.2 \times 10^9/L$) were both significantly lower for INTERCEPT-platelet recipients when compared to those transfused untreated cells. However, the median time to the next transfusion was not significantly impacted. No differences in adverse events or transfusion reactions were observed.

The EFFIPAP trial aimed to compare the effectiveness of platelets in PAS, treated with INTERCEPT vs untreated platelets in either plasma or additive solution, in patients with thrombocytopenia or hematological malignancies [18]. The primary endpoint was Grade 2 or higher WHO bleeding, with a noninferiority margin of 12.5 %. Primary end point was observed in 47.9 % of patients with PRT + PAS, 43.5 % of patients receiving platelets in plasma, and 45.3 % in platelets + PAS. Noninferiority was not achieved by PRT-PAS platelets (absolute risk was +4.4 %) but was achieved by PRTs + PAS vs platelets in PAS alone. Incidence of grade 3 and 4 bleeding was comparable across all groups. Patients receiving PRT + PAS received significantly more transfusions (median 6, IQR 4–9) than patients receiving platelets in plasma (median 5, IQR 2–7, $p < 0.001$), but not compared with patients receiving platelets + PAS (median 5, IQR 3–8, $p = 0.17$). PRT + PAS recipients were more likely to receive a second platelet transfusion in under 2 days after the first transfusion (31.6 %) compared with patients in the other treatment arms (platelets + plasma 13.2 %, platelets + PAS 15.2 %, $p < 0.001$ for both tests). Mean 24 h CCI after first transfu-

sion was significantly lower for PRT-PAS (5.0) compared with the other 2 arms (10.2 platelets in plasma, 8.2 platelets in PAS). Treatment failure also occurred more frequently in PRT + PAS recipients.

A few meta-analyses have investigated the results of the listed clinical trials. The most consistent finding is that transfusion of INTERCEPT-platelets is associated with a significant decrease in 1 h and 24 h CCI [13,14]. A shortened interval between consecutive platelet transfusions was also found in INTERCEPT- vs untreated platelets [13]. In contrast, there appears to be no statistically significant difference in the frequency of WHO-grade bleeding events between INTERCEPT- and untreated platelets. However, it should be noted that this finding is inconsistent: Depending on which studies are included, and whether expanded safety analysis data is considered instead of the initial reports collected during the studies, increases in clinically significant bleeding with regards to INTERCEPT-treated platelets are indeed found. Two recent post-marketing surveillance studies have both returned that INTERCEPT-platelets have a CCI that is not statistically different from reference platelet concentrates [19,20]. However, it is difficult to draw conclusions at this time.

Pathogen reduction technologies are clearly here to stay. What we now need are licenced technologies that can be used to treat red blood cell concentrates. These are under consideration in several jurisdictions and the Mirasol whole blood treatment has been approved for use in Europe.

Other novel products coming to transfusion medicine

Platelet wastage rates can be a problem in some jurisdictions. One way to address this is to use cold stored platelets for bleeding patients. Another strategy is to freeze platelets for subsequent use in bleeding patients; this is particularly an attractive option for rural transfusion medicine. Neither of these products can be used for prophylactic platelet transfusions as the platelets are rapidly cleared from the circulation [21].

Whole blood is now considered to be the preferred resuscitation fluid for air ambulance services. Clinical data clearly show that patients receiving whole blood have a lower mortality rate than those who receive other options [22].

There is a renewed focus on blood product quality. This focus is likely to lead to altered donor management approaches. Numerous labs are currently looking for biomarkers that identify poor storing donors. One can envision a time where these donors will be screened for these biomarkers and managed to ensure that they give the product that they have that keeps the highest quality [23]. This may mean less whole blood collection in favour of sending donors to donate plasma.

Conclusion

The landscape of blood components is heavily influenced by advances in safety practices, implementation of novel technology, and the efficacy of new transfusion products. Presently, the principal change in the field is the rollout of PRTs, which promise to significantly improve the safety of platelet transfusion, both in terms of TTIs and immune reactions. However, the diminished transfusion efficacy of PRT-PCs suggests that platelet demand may increase, further straining the already tenuous platelet supply. While other PRTs are currently under review, they also depend on UV-irradiation and thus apply the same strain on platelet supply. Fortunately, alternative products such as cold-stored platelets and whole-blood transfusion packs are re-emerging, and hold promise for treatment of major bleeding. Furthermore, increased understanding of donor variability with regards to transfusion effi-

cacy and storage requirements, may result in novel strategies to optimize blood banking and personalized transfusion needs.

Declaration of Competing Interest

DD is the chief scientist for Canadian Blood Services; chairs the scientific advisory board for Macopharma, Mouveaux, France; serves as the president of AABB; and sits on the board of directors of STRM.Bio, a gene therapy start-up, Boston, Massachusetts.

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