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Research Article

Plasma Reduced Platelet Concentrate's Hidden Face: Platelet Traps

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Abstract

Transfusion of platelet concentrate (PC) can be the cause of allergic side effects triggered by plasma constituents. To prevent such reactions, residual plasma is reduced and replaced with a substitute solution such as Intersol®. Plasma proteins are largely eliminated (the level of residual extracellular proteins should be less than 0.5 g per product), reducing the risk of allergic reactions by up to 70%. Faced with a drop in platelet yields and the quantity of active products (QPA) following plasma reduced CP in 2022 at the EFS PACA Corse IH-DEL site in Nice, we carried out a causal analysis using the 5M method.

The initial quality of CP was assessed: age before processing, QPA and initial volume. The equipment and supplies used were checked, as was the sampling process. The human resources used for processing were analyzed. Compliance with the plasma reduced PC procedure and critical steps were examined through a survey of authorized technical staff.

This survey revealed a disparity in the application of the processing procedure leading to platelet loss through "platelet traps". We thus identified stages at risk of the method. Revalidation of the plasma reduced PC process was carried out on 5 PCs in 2023. The quantity of residual protein in the product, the final QPA and the platelet yield were all found to be compliant. The drift in platelet yields after the deplasmatization of CPs in 2022 in the Nice lab provided an opportunity to review practices and raise awareness about platelet traps.

Keywords: Platelet Trap; 5M Model; Plasma Reduced Platelet Concentrate

Abbreviations

EFS: Etablissement Français Du Sang (French Blood Establishment); HAS: Haute Autorité de Santé (French National Authority for Health); LBP: Labile Blood Product; MPV: Platelet Size; NTH: Non Therapeutic; PC: Platelet Concentrate

Introduction

Platelet concentrate transfusion could cause anaphylactic reactions. According to the French Haemovigilance 2022 annual report, allergic reactions were the second most frequently reported adverse reaction[1]. These involved exclusively mild

to moderate reactions such as pruritis, rashes, or urticaria. Reporting rate was 108,8 per 100 000 labile blood products (LBP) transfused in adults and 20,7 per 100 000 LBP transfused in pediatric patients [1]. The risk of allergic reactions is between 0,09 and 21% in patients [2,3], with figures varying by series [4]. In literature, allergic reactions are also highly variable in severity [3]. In addition to dermal manifestations, systemic reactions may include bronchoconstriction, hypotensive reactions and shock [3]. It could be caused by plasma constituents such as food allergens or inflammatory cytokines [5]. IgA-related anaphylactic reactions occurring in patients with IgA antibodies are described but seem over-diagnosed [6]. To prevent these manifestations, plasma-reduced PC appears to be a safe and effective approach [7,8]. Several guidelines recommend this technique for patients who have experienced recurrent transfusion allergic reactions or anaphylactic shock [5,9,10]. Plasma is replaced by a substitute solution such as Intersol®. Plasma proteins are removed, and residual extracellular protein is expected at below 0.5g / product [11,12]. This technique may reduce anaphylactic reaction up to 70% [13]. PC's quality control for each transformation is performed by platelet yield and a measure of final platelet count. However, the indication of plasma-reduced PC must be well thought out. Plasma-reduced PC manipulation induces activated platelets and causes a diminished increase in post-transfusion efficiency. The other negative point is the reduction in PC life to 6 hours.

In the Nice Etablissement Français du Sang (EFS) center, plasma-reduced PC is carried out according to the HAS recommendations [9], i.e. in case of a background of major anaphylactic reactions, life-threatening or moderate reactions and repeated reactions if it is a barrier to transfusion. Another indication is IgA deficiency associated with IgA antibodies. In 2022 we observed a progressive decrease in platelet yield and final platelet count in our plasma-reduced PC (Figure 1). To explore this, an analysis of causes using the 5M model has been done. Thanks to this analysis, we detected platelet trap in our procedure.

Materials and methods

Platelet concentrates

Platelet concentrates were obtained with apheresis systems or whole blood from healthy donors according to French guidelines

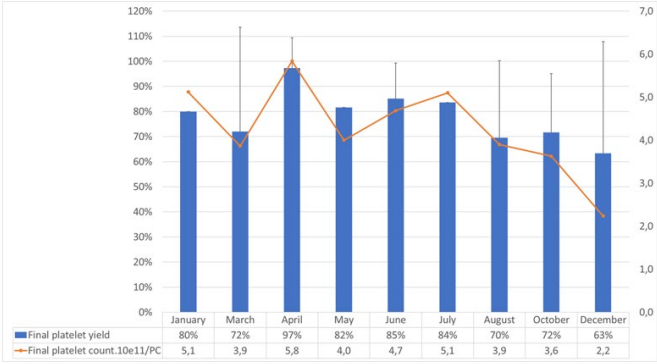

Figure 1: Plasma-reduced platelet concentrate (PC) alteration during the 2022 year. Histogram (blue) shows the decrease in the platelet yield average after plasma-reduced PC falling below the 80% specification. Curve (red) shows the decrease in final quantity in platelet (10e11) per product. Minimum platelet quantity is 1.5.10^{e}11/PC.

[11]. Products were leukoreduced and had pathogen inactivation thanks to UVA and amotosalem®. Both non-therapeutic and therapeutic apheresis PC and compound PC were used in the revalidation process. Products contained at least 2.10^{e}11 platelets [12]. PC were stored in bags (Cerus corporation) and conserved between 20 and 22°C with constant agitation.

Plasma reduced platelet concentrate preparation

Four steps were necessary for plasma-reduced PC. First, PC were transferred to a transfer bag (Macopharma) thanks to sterile connection then centrifugated for 10 minutes 2050g at 20°C. Then, plasma was extracted using a manual press and replaced with Intersol® preservative solution (Fresenius kabi).

Quality control

Platelet concentration was measured with a hematology analyzer (Advia2120i-Siemens). Plasma proteins were dosed with the Bradford method (Bio-rad) on plate reader AMR 100-Allsheng. PC swirling, platelet aggregates and color change in PC were examined before and after transformation. Plasma-reduced PC must contain at least 1,5.10^{e}11 platelets and less than 0,5g of proteins [12].

5M analysis

Equipment and supplies used were verified. Compliance with the procedure was examined by means of authorized technical staff survey. Using the Mann-Whitney test, we compared our products before transformation between 2021 and 2022: PC age, and the initial amount of active product (platelet count x volume) and initial volume (mL). Lastly, we reviewed the sampling method for quality control: procedures, used sample bags and storage prior to platelet count in the quality control lab.

Results

Materials and Equipment were compliant

The equipment and supplies used were well-maintained and operational. The centrifuge temperature was checked at rest and during operation. Supplies were compliant.

There were no significant differences in PC quality before processing between 2021 and 2022 : age of PCs on the day of processing and the day of quality control at the quality control lab (respectively p=0,13 and p=0,66), initial volume (p=0,69) and initial amount of active product (p=0,08).

Platelet trap identification and revision process required

All technicians were qualified and experienced. However, departmental activity was sustained in the second half of 2022 during a period of understaffing.

A survey of the technical team revealed a disparity in the application of the processing procedure. Manipulations leading to platelet loss were not controlled. Placing the PC bag is a delicate step and wedges limit folding of the bag during centrifugation. Only a few technicians used wedges. After centrifugation, half of the team placed the CP on the bench top as it was being transferred to the collection bag, with the risk of resuspension of the platelet pellet, while the other half left the product in the pad. Finally, the preservative solution was added rapidly in one go, risking platelet aggregation. Therefore, we have highlighted the "platelet trap" stages, in particular when folding the bag. Figure 2 shows them and the recommendations to be followed.

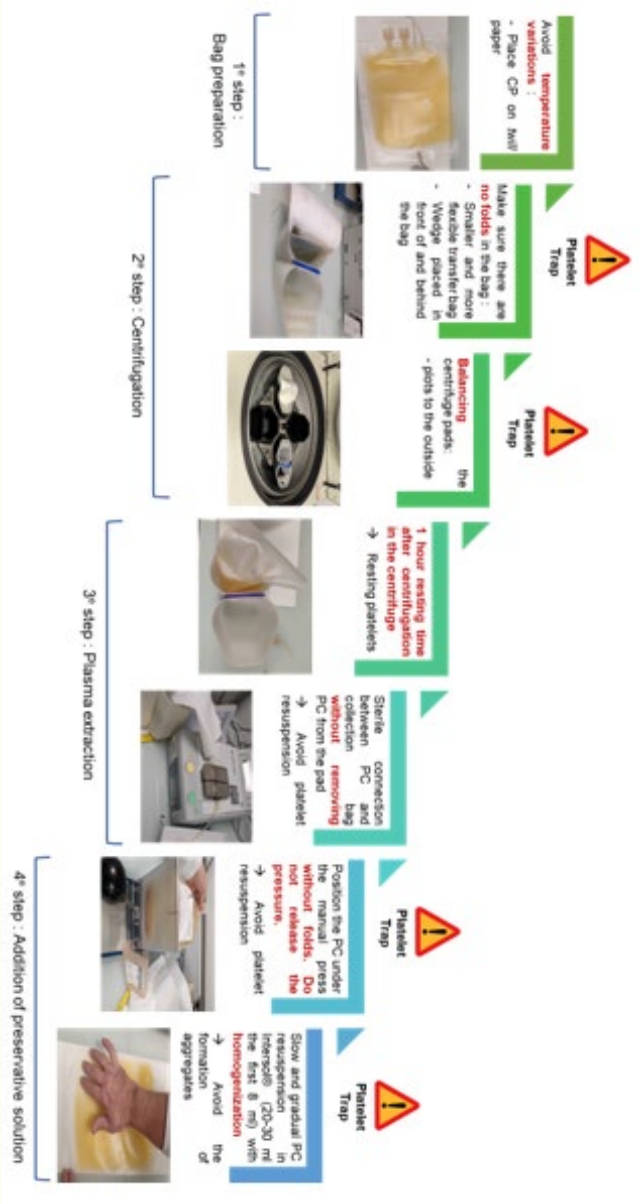

Figure 2: Shows precautions to avoid platelet loss through « platelet traps » during plasma reduced PC process.

We identified bias in the quality control process : PCs were not homogenized before sampling. In addition, the bag used to transfer platelet sample to the quality control lab was not suitable for storage, and some platelet counts were taken 24 hours after handling.

Validation of the new method

After training, we revalidated the plasma-reduced PC process on 5 PCs in Q1 2023 (table 1). Samples were taken on EDTA tubes after several turnovers. The quantity of residual protein in the product, the final QPA and platelet yield were all found to be compliant. All plasma-reduced PC had swirling, no platelet aggregates and no color change after transformation.

PC	Number	Minimum platelet count	Platelet yield	Extracellular protein	Conclusion
Expected value		≥ 1,5.10^{e}11	> 80%	≤ 0,5 g/U	
NTH PC	1	4,03	81	0,27	CONFORM
NTH PC	2	3,82	83	0,1	CONFORM
NTH PC	3	4,69	85	0,45	CONFORM
NTH PC	4	3,3	84	0,11	CONFORM
NTH PC	5	2,76	99	0,16	CONFORM

Table 1: Shows the revalidation of the plasma-reduced platelet concentrate (PC) process with 5 non-therapeutic compound PC (NTH PC).

Conclusion

Platelet concentrate transfusion is an important supportive therapy. Unfortunately, transfusion of plasma-containing blood components may be associated with a variety of allergic-type reactions, ranging from a few hives to life-threatening anaphylaxis [6]. One of the most effective approaches used to avoid allergic-type reactions is plasma-reduced PC before transfusion [6,9,14].

The decrease in platelet yields after plasma-reduced PCs in 2022 in the EFS department at Nice provided an opportunity to review practices and raise awareness about "platelet traps". We used 5M analysis to carry out an exhaustive investigation. We investigated PC quality before processing. Moreover, we checked the equipment, materials and consumables used. Finally, we assessed the technical team's compliance with the procedure.

Thanks to the survey, we have identified the platelet trap steps in the procedure. The most sensitive points for improving platelet yields were found to be: the initial transfer of CP to a smaller bag, the use of a more flexible transfer bag for easier insertion into the centrifuge plots, and the gradual resuspension of Intersol® with continuous homogenization. The position of the wedges around the PC bag in the centrifuge pad is also critical to avoid bag folds.

In our study, we didn't mesure the platelet size (MPV). Modification in MPV could be caused by shape change of the platelet from discoid to spherical shape and thus modify their anti-aggregating activity. During the validation of the new method, we could have observed an impact or lack thereof on the MPV.

Plasma-reduced PC has been shown in previous studies to result in a 4% to 40% loss of platelets [15]. According to French regulation, after plasma-reduced PC transformation, loss of platelets should be below 20%. Our revalidation process was a success, both in terms of platelet yields and the quantity of protein expected, but on a small number of products. However, as seen in the various loss of platelets described in the literature, it would be interesting to work on a larger amount of PC to optimize this procedure applicable to different countries.

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