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Storage of Platelet Concentrates - Looking Beyond Standard Parameters for Prolonged Storage

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Abstract

The recommended quality guidelines for storing Platelet Concentrates (PCs) is for up to 5 days at a temperature of 22°C ± 2°C, with constant agitation. This short storage life is problematic since the demand for therapeutic use of PCs has increase and blood establishments may occasionally struggle to meet such demands. This storage life is owed to increased susceptibility to bacterial contamination, as bacteria thrive in these conditions, and due to platelet storage lesions, as platelets and white blood cells remain metabolically active. Guidelines recommend that increasing PC storage should only be feasible if bacterial screening is performed prior release of such units. Such guidelines do not however take into consideration other factors such as cytokines. Cytokines cause transfusion-related reactions and concentrations may change over the storage life due to metabolically active cells. This review aims to provide insight on additional quality parameters one might consider when prolonging platelet shelf life.

Introduction

Platelets are small, disc-shaped, anucleated fragments from megakaryocyte cytoplasm with an average physiological lifespan of 10 days. The main function of platelets is to maintain hemostasis and prevent excessive hemorrhage [1]. Given their function, Platelet Concentrates (PCs) are used as prophylaxis or treatment in individuals with acquired or inherited platelet function disorders and in cases of thrombocytopenia, particularly those patients undergoing chemotherapy or with hematological malignancies [2]. Moreover, PCs contain growth factors that have been employed to promote the growth of several tissues [3]. All things considered, the need for PCs has increased over the years due to increased life expectancy and increased use of targeted therapy [4]. The availability of these units is highly dependent on voluntary blood donors and strict regulations to ensure the safety of the blood products may further hinder such availability. Therefore, due to the combination of the increased demand and the regimens in place for recruitment of blood donors and quality controls performed, the availability of these units is a constant issue. European Union countries are bound to adhere to the quality standards set by the European Directorate for the quality of Medicines and Healthcare (EDQM). These parameters aim to increase the platelet count in patients but fail to provide guidance on platelet functionality and other possible adverse events caused by other factors related to Platelet Storage Lesions (PSLs).

Platelet Storage Lesions

Morphological, functional, and metabolic changes in PCs are collectively called PSLs. The changes begin during collection and continue to develop during processing and storage [5]. Following the EDQM [6], PCs should be stored at a temperature of 22°C ± 2°C, with constant agitation for up to 5 days. Some institutions may opt to store PCs for up to 7 days if appropriate tests to detect bacterial contamination are completed before releasing the unit to the patient [6]. It is important to recognize and investigate these lesions when increasing the shelf-life of PCs to 10 days, to ensure that therapeutic efficacy is maintained. The pH of PCs should be maintained above 6.4 for platelets to remain viable. Metabolites produced from platelet metabolism alter the pH of the environment, which causes a change in platelet morphology and decreases their survival post-transfusion. Over the years, various strategies have been introduced to reduce the formation of PSLs. Advances in the scientific field have seen the development of new storage media such as Platelet Additive Solutions (PAS), which replaces the use of plasma during the preparation of platelets [7]. PAS acts as a buffer and provides additional nutrients for the longer survival of platelets, thus allowing for a longer storage

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life. Hornsey et al. [8] analyzed the quality parameters (platelet count and indices, platelet activation and metabolic tests) of PCs stored in PAS, namely SSP+, at 22°C for 19 days and found that the quality was maintained up to 9 days. Bashir et al. [9] compared PCs stored in plasma *vs.* PAS at 22°C for 10 days and found that quality levels were maintained for up to 10 days in PAS but were only sustained for 5 days in plasma. However, there was no significant difference between the concentrations of lactate dehydrogenase in the two cohorts [9]. Another mitigation to try and reduce PSLs was the introduction of constant agitation and gaseous-permeable bags, which filtered the CO2 produced by the metabolism of platelets and more importantly prevent the depletion of O_2 [10]. Furthermore, MacLennan et al. [11], studied the therapeutic efficacy in PCs stored for 6 to 7 days in patients with hematological malignancies and compared them to PCs stored for 2 to 5 days. The authors found that both shelf lives provided equivalent therapeutic efficacy and risk of transfusion reaction if PCs are screened for bacteria [11]. Therefore, increasing the shelf-life of PCs, if therapeutic efficiency is maintained, should be feasible with bacterial screening or inactivation of bacteria [12].

Platelets generate ATP through glycolysis and oxidative phosphorylation. The requirement for ATP increases as platelets aggregate and become activated, thus there is an increase in oxidative phosphorylation as this is more efficient at generating ATP [13]. However, in the absence of oxygen pyruvic acid is converted to lactic acid and this makes the environment more acidic [14-16]. This is problematic as it causes more platelet activation, which leads to changes in platelet morphology and Glycoprotein (GP) expression, as well as degranulation, leading to aggregation and increased risk of transfusion reactions [5].

The gold standard for measuring platelet activation is through flow cytometry using markers such as p-selectin (CD62P), which is released from α-granules and expressed on the platelet surface [17]. However, there are conflicting data with regards to the relationship between activation of platelets and post-transfusion recovery. Some studies observed that an increase in CD62P *in vitro*, correlates with a decrease in post-transfusion recovery, while other studies showed that there is no correlation between the two [18-21].

The function of platelets can be assessed using hypotonic shock response, which measures the ability of platelets to undergo biochemical and enzymatic changes after being subjected to a hypotonic solution [22]. The discoid shape in response to ADP can be measured using the extent of shape change and both of these tests have been shown to correlate well with platelet viability [23]. A more practical assessment of function and morphology is by analyzing platelet indices such as Mean Platelet Volume (MPV) and Platelet Distribution Width (PDW) [24]. MPV together with PDW can be used to determine if there is an increase in platelet volume distribution, which corresponds to PSLs [25].

Alterations in Cytokine Concentration with Storage Time

Febrile Non-Hemolytic Transfusion Reactions (FNHTRs) are defined as an increase in body temperature of 1°C or more, chills and/or rigor post-transfusion (up to 4 h) without hemolysis [26]. FNHTRs were thought to be caused by anti-HPA or anti-HLA antibodies, and although this may sometimes be the case, it does not always correlate with the clinical picture because a sensitization stage is not always evident [27]. Muylle et al. [28] investigated the levels of cytokines in PCs and reported that PCs with higher concentrations of contaminating WBCs had higher levels of cytokines. Moreover, they monitored the outcome of recipients and found that despite post-storage leucoreduction, some recipients still experienced FNHTRs [28]. This and other studies suggest that cytokines in blood products induce FNHTRs or even more severe reactions such as Transfusion-Related Acute Lung Injury (TRALI) and transfusion-related immuno-modulation [29,30].

Sources of cytokines in platelet concentrates

Cytokines in PCs increase significantly during storage from metabolically active or lysed WBCs [31]. FNHTRs are more common in PCs due to the storage temperature of these units, as WBCs and platelets remain metabolically active [32]. Therefore, leucoreduction not only decreases WBCs, but also decreases the production of cytokines during storage [33]. Pre-storage leucoreduction was found to be more effective than post-storage leucoreduction or gamma-irradiation at decreasing the levels of cytokines in PCs [29]. This suggests that cytokine levels increase during storage, and levels are dependent on the method of preparation [34]. Klüter et al. [35], studied the effect of pooling together Buffy coats from four different donors to see whether the WBCs from different donors stimulate the release of cytokines and they found that this did not affect cytokine concentration. Cytokines may also be in abundance in blood products donated from individuals that are predisposed to chronic inflammation such as those with type 2 diabetes [31,36]. Hartwig et al. [37] studied the levels of cytokines in Buffy Coat-derived PCs (BC-PCs) with different WBC counts and found a positive correlation between WBC count and cytokine concentrations. They also noted that even with pre-storage leucoreduction, the levels of the cytokines Interleukin (IL)-1β, IL-6, IL-8, and Tumour Necrosis Factor- α (TNF-α) increased over the 5 days of storage due to residual leucocytes [37]. Moreover, leucoreduction does not affect platelet-derived cytokines such as Transforming-Growth Factor-β (TGF-β), which increases during storage [38].

Interleukin-6

IL-6 is a pro-inflammatory cytokine responsible for several functions of the immune system. It is released from WBCs and other cells upon stimulation by various molecules, including other cytokines such as TNF-α [39]. IL-6 is involved in the differentiation of B-lymphocytes leading to the production of antibodies, differentiation and proliferation of T-lymphocytes and hematopoiesis [40]. Its predominant function is to enhance inflammation by stimulating the production of acute-phase proteins, leading to a systemic effect such as fever and increased vascular permeability [41]. Muylle and Peetermans [42] found that the levels of IL-6 did not increase in BC-PCs, during storage time in Plasmalyte A. Other studies found that the immunoassay levels of IL-6 were below the limit of detection in leukoreduced BC-PCs during the 5 days of storage, while others showed an increase in IL-6 up to 9 days of storage [29,34,43]. Wadhwa et al. [44] investigated the levels of IL-6 and other cytokines using bioassays to determine whether these are biologically active. IL-6 was found to be biologically active, and the levels remained constant in unfiltered BC-PCs and Apheresis PCs (A-PCs), but levels were undetectable in leukoreduced BC-PCs [44]. The biological activity of IL-6 is further supported by other studies showing that the risk of FNHTRs increased with increased levels of IL-6 [45-47].

Tumour necrosis factor-α

TNF-α is another pro-inflammatory cytokine released primarily

from monocytes and macrophages but can also be released from other cells of the body [48]. This cytokine has some analogous effects to IL-6, as it provokes a systemic response and activates other cells to support and enhance inflammation. Thus it plays a crucial role in infectious diseases and it can also stimulate cells to undergo necrosis or apoptosis [49]. TNF-α is a potent cytokine as even low levels in the blood can lead to fever, chills, and systemic shock [50]. Muylle et al. [28] tested the levels of cytokines in unfiltered PCs and found that TNF-α increased significantly with increased storage time and increased WBC count. This increase in TNF-α level was correlated with increased risk of FNHTRs [28]. However, several studies reported that the levels of TNF-α in leukoreduced BC-PCs and A-PCs were undetectable or insignificant even up to 9 days of storage [21,34]. Wadhwa et al. [44] reported that increased levels of TNF-α were detectable on day 5/6 but these had no biological activity as they were inactive.

Transforming growth factor-β

TGF-β is mainly secreted by activated platelets and has counteracting functions, as it can enhance and inhibit inflammatory processes [51,52]. This cytokine facilitates wound healing and WBC chemotaxis, induces the release of cytokine from monocytes, but suppresses hematopoiesis and proliferation of cells in the bone marrow [53]. Wadhwa et al. [54], investigated the levels of TGF-β using immunoassays and bioassays, and these correlated with each other. They found that the levels of TGF-β on day 1 were markedly higher in A-PCs than BC-PCs, which could be due to increased activation of platelets in A-PCs during collection [44]. Thus, this can be used as an indirect marker of platelet activation and/or damage. On day 5/6 the levels of TGF-β increased 2-fold in BC-PCs and 3-fold in A-PCs [44]. Furthermore, the levels of TGF-β were slightly higher in leukoreduced BC-PCs when compared to unfiltered BC-PCs signifying that filtration might cause platelet activation [44]. Studies also found that the levels of TGF-β and other platelet-derived cytokines increase during storage time regardless of the leucoreduction method used [54]. Kunz et al. [55] studied the levels of TGF-β in stored A-PCs and BC-PCs for 5 days and in recipients with hematological malignancies before and after platelet transfusion. On the contrary, they found that the levels of TGF-β were slightly higher in BC-PCs than A-PCs during storage time, which could be due to the different apheresis machines used [44,55]. The levels of TGF-β in healthy donors were low, which further confirms that the levels increased during storage and the levels in recipients between pre-and post-transfusion increased by an average of 36% [55]. However, the effects of transfusing TGF-β are not predictable as the molecule is multi-factorial [56].

Prolonging Platelet Storage

The safety and efficacy of PCs are both key factors when taking into consideration the possibility of prolonging shelf-life. Studies have reported no association between storage duration and morbidity or mortality when leucoreduced platelet units are transfused [57,58]. Furthermore, quality parameters that determine if such units can be transfused are within requirements [23,59]. Aubron et al. [58] report prolonged stored platelets as a possible treatment for patients with no hematological complication, but do not exclude other implications if the product was to be used on patients with systemic inflammatory diseases. Such an adverse outcome was discussed by both Kreuger et al. [57] and Losos et al. [60], and seen also *in vitro* through complement activation by Chen et al. [61]. However, Fiedler et al. [23] and Javed et al. [62], mitigate that platelets are still viable after prolonged storage. A higher platelet *in vivo* clearance is observed when platelets that are older than 3 days are transfused [57,58]. However, reports indicate the hemostatic function of prolonged cold-stored platelets is similar to that of traditionally stored units [63]. Furthermore, Hegde et al. [64], do not recommend the use of cryopreserved platelets or that platelets treated for pathogen reduction be used in patients with hematological disorders while Waters et al. [65] report successful use of such units in the treatment of bleeding.

Literature suggests that storage time and temperature might trigger adverse events [57,60,61] and might not be as effective on patients suffering from hematological malignancies [64] but are effective in treating bleeding [62,66]. Studies have also shown that quality requirements for prolonged stored PCs were deemed acceptable [23,59] and that these units retained functionality [23,62]. To this end, strong emphasis is being made to include platelet functional assays to the list of parameters that determine the quality of platelets for transfusion [66,67].

Conclusion

Managing the demand for PCs is not easy as this may vary on daily basis. Although erring on the side of caution and producing more units than effectively necessary may be justified, this eventually leads to wastage of resources and does not guarantee that the demand of any given day will be easily met. To meet the continuous increase in the demand for PCs, the option of prolonging platelet storage is the way forward. Since directives do consider platelets stored for up to 7 days as being effective, the main issue for implementing this is ensuring the control of bacterial contamination. Without compromising the safety and quality of blood products, new strategies need to be developed to meet the constant increase in demand of this blood product. Platelets have a physiological lifespan of approximately 10 days, so increasing the storage time might be feasible. However, due to the storage conditions of these units, PSLs and bacterial contamination are problematic and need to be studied before prolonging the shelf-life. Cytokine levels also need to be investigated as these may increase during the storage of PCs from metabolically active residual leucocytes and increase the risk of FNHTRs and TRALI.

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