Conversion from Platelet-Rich Plasma Platelet Production to Buffy Coat Platelet Component Production: Benefits and Limitations

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Abstract

Blood transfusion centers are under considerable pressure to produce platelet concentrates with high quality and safety due to the short shelf life of 3-5 days as well as possible bacterial and viral contaminations. For a variety of reasons, many Europeans have changed their methods of component production from whole blood using the North American standard platelet-rich plasma method to the buffy coat method of platelet production. Many advantages and some limitations during conversion from platelet-rich plasma method to buffy coat method have been observed. It seems that decisions to switch from platelet-rich plasma method to buffy coat method with whole blood component production should be considered; the benefits from increased platelet yield, improved platelet quality, increased plasma recovery, reduced blood transfusion adverse reactions and lower pathogen transmission rates compared to the platelet-rich plasma method outweigh any transient difference in red cell parameters or inconsiderable reduction of factor VIII activity. The purpose of this review is to discuss the quality, safety and economic aspects of blood components production during conversion from platelet-rich plasma to buffy coat method in preparing blood components which may benefit developing countries.
Keywords: Buffy coat, platelet-rich plasma, platelet concentrates, blood components.

Introduction

Blood transfusion centers are under considerable pressure to produce platelet concentrates (PC) with high quality and safety due to the short shelf life of 3-5 days as well as possible bacterial and viral contaminations. One of the approaches to solve the shortage of platelet concentrates is using platelet substitutes such as infusible platelet membrane[1-6], lyophilized platelets [7] and other similar products; but conversion from conventional production process of PC to the new buffy coat (BC) method is the more feasible approach. Many blood transfusion centers have changed their methods of component production from whole blood using the North American standard platelet-rich plasma (PRP) method to the BC method of platelet (PLT) production. The change arose from dissatisfaction with the infranatant RBCs left after the removal of PRP. They were heavily contaminated with white blood cells (WBCs), which caused febrile,

nonhemolytic transfusion reactions[8]. Furthermore, PLTs and WBCs contributed to the formation of microaggregates in the RBCs, which were thought to be deleterious for the recipient[9]. BC method was developed by investigators in the Netherlands and Sweden in the mid-1970s[10]. At the present time, this method is used predominantly in Europe, Canada and most of the Latin America countries, except USA. The aim of this study is to describe quality, safety and economic aspects during conversion from PRP method to BC method in preparing blood components which may benefit developing countries.

Methods of platelet pre-paration

In the early 1960s, PRP was used without further manipulation to reduce the incidence of hemorrhage in thrombocytopenic patients[11]. In that period, blood was processed under refrigeration,

and irreversible platelet clumping was observed when efforts were made to concentrate the platelets further with a hard spin. This problem was solved in the late 1960s by dual modification of processing the blood and PRP at room temperature (22°C) and holding the sedimented platelets stationary for 30 to 60 minutes before resuspending them as a platelet concentrate [12]. This method of production has been remained as a standard platelet component production method in the United States and many other countries since then.

The BC production method reverses the sequence of centrifugation steps compared to PRP. A hard spin is used initially to separate whole blood into three components: plasma, red blood cells (RBCs), and a BC layer. Using semiautomated extraction, the most common configuration uses a so-called top-and-bottom collection set in which plasma and RBCs are transferred to storage containers and the BC is left in the donation bag. This BC contains platelets, white blood cells (WBCs), plasma, and some RBCs. ABO-matched BCs are pooled together with one plasma unit from one of the donors or one unit of platelet additive solution using a sterile docking device. The pooled BC is then given a soft spin, and the PRP is extracted with or without leukofiltration to produce a pooled PC. Although both methods produce a platelet product, the products may have somewhat different in vitro characteristics [13].

Quality aspects of blood component products
Platelet concentrate

There is a remarkable quality improvement in laboratories marking platelets using buffy coat (BC-PC) method relative to platelets produced by PRP (PRP-PC) method [10,13-16]. The second centrifugation in the preparation of PC in PRP-PC method is associated with reversible platelet aggregation and contact with non-biological surface, which probably is induced by activation due to the close contact between platelets in the platelet pellet while, BC-PC method does not involve significant close cell contact between platelets in a pellet. In addition, PRP-PC method may stimulate more degranulation or activation during hard spin centrifugation without the presence of WBC and RBC as a barrier "biologic cushion" to lower these stresses. Some studies considering the BC-PC method have indicated lower platelet activation

(P-selectin or Annexin V) [13,15-23], higher morphology score [13,21,23,24], equal or better extend shape of change (ESC) and hypotonic shock response (HSR) [13,23,25], higher pH [13,20,22,25], lower residual WBCs [13,20-22,26] higher platelet yield [13,14,21,22,26-29], better aggregation response to ADP [21,30,31], higher recovery and survival [22,25], lower bacterial infections [32-37], lower release of α-granular contents 38-40, higher glucose [41], lower contaminated RBC [31] and higher total ATP [23] in comparison with PRP-PC method. But, there are some other studies that show no significant differences between the two methods in platelet activation such as P-selectin or annexin V[22], WBC residual [31], pH [22,20,21,42], extend shape change (ESC) 22,42, hypotonic shock response (HSR) [22,31,42], morphology score [31,42], glucose [22,42], lactate [22,42], ATP[21,42], PO2 and PCO2 [21,42], platelet yield [20,26,28,40,43,44], corrected count increment (CCI) [45-47], recovery and survival [22,26,42,48], RBC contamination [20] and even bacterial contamination [49,50] in BC-PC method.

In general, there is more evidence that indicate noticeable quality improvement in laboratory markers of BC-PC relative to PRP-PC.

Packed red blood cells

One of the major aims of BC removal was the improvement of RBC quality. In fact, it cannot be claimed that this improvement was completed, particularly considering the recent technical advances. There are some disadvantages of BC-PC method that have been reported for packed red blood cells such as loss of RBC about 10% or more [43,51], lower survival [52], lower 2,3-diphosphoglycerate [53-59] (2,3-DPG), lower pH [54,60,61], lower bicarbonate concentration [54], higher lactate [54], lower glucose [54], lower viability [62-66], increase in the volume of RBC [67], significant increase in the number of residual WBCs in the 24-hold RBC units [68] and lower post transfusion recovery [69].

The most important concern associated with the overnight storage of whole blood (WB) is the significant increase in the number of residual WBCs in the 24-hour RBC units. Several researchers have demonstrated that RBC unit temperature, age and the number of residual platelets considerably influence the leukoreduction efficiency of RBC units [70-80]. Albeit, WBC reduction in these studies, was performed on WB donations or on RBC units obtained by the BC method or within 8 hours of

collection in PRP method. Due to these problems, investigations concerning the effects of simple operational modifications such as decreasing the temperature of RBC units before leukoreduction, increasing the filtration time and optimizing centrifugation steps are being continued. It is noteworthy that when WBCs are exposed to the acidic conditions of storage and refrigerated in red blood cells concentrates, they respond with activation and cytokine production before they die [81]. After they die, the WBCs break down and release constituents including enzymes such as phospholipase-A2. Phospholipase-A2 in turn attacks and breaks down phospholipids released by red blood cells, creating lysophospholipids such as the dialkyl glycerol platelet-activating factor. The longer the red blood cells are stored, the more of these biologically active lipids are produced. Leukoreduction of red blood cell concentrates shortly after collection markedly reduces the concentrations of lysophospholipids. Leukoreduction also decreases the changes that cause stored red blood cells to stick to endothelial cells in culture and probably to post-capillary venules in the circulation [82]. Five years of follow-up in France has shown significant less residual WBCs in red blood cells concentrates after leukoreduction [83].

Today, by using improved systems based on Top and Bottom (TAB) technology, adequate adjustment of the centrifugation and fractionation system configuration parameters can compensate RBC loss affording maximum yield from each donation and the production of blood components of increased quality [28, 84,85]. On the other hand, a use should be found for these lost RBCs in BC-PC method. They could be used for the preparation of therapeutic hemoglobin solutions. In addition, these low density RBCs are enriched with young reticulocytes (neocytes). These cells are less dense than older red cells and will end up in the upper layer of the red cell fraction. Transfusion of neocytes can prolong the interval between transfusions in chronically transfused patients [86-88].

Frozen plasma

The subject of method of production of plasma for transfusion has received relatively little consideration. In organizations that fractionate derivatives such as IVIG or factor VIII (FVIII) from plasma, the efforts are generally conducted to recover the maximum amount of plasma with maximum functional activity. The production of transfusion plasma from the whole blood uses either a shortened production time to prepare so-called 'fresh frozen plasma' or a longer production time to produce a routine frozen plasma product. Reports indicate that these products are not so very different from one another with respect to the functional activity of coagulation and anti-coagulant proteins [53,89,90].. The characteristics of frozen plasma which is prepared 24 hours at room temperature before freezing has demonstrated similarity to fresh frozen plasma , except for a 15% to 20% reduction of FVIII [91,92]. Sheffield et al. between 2006 and 2008 observed neither significant reductions in fibrinogen, factor V, ABO-matched FVIII or antithrombin, nor prolonged APTT or PT results when comparing frozen plasma derived by BC (FP-PC) to frozen plasma derived by PRP (FP-PRP) method [93]. No differences have been observed by other studies among FP-BC, FP-PRP or FFP, with exception of the well-known reduction in FVIII activity that supports longer times between donation and freezing [68,94-97].

Safety of blood components
Adverse reactions to transfusion

It has been shown that the use of PRP-PC is much more associated with adverse reactions in recipient than BC-PC [98-100], and their occurrence is strongly correlated to the amount of IL-6 in PC [98]. In addition, no significant increase in the levels of TNF-alpha is observed in BC–PC during storage period, while levels increase significantly in PRP–PC on day 1 [101]. Febrile non-hemolytic transfusion (FNHTR) reactions are the most common adverse reactions to platelet transfusions [102].

The frequency of febrile or urticarial transfusion reactions have been reduced by using BC method and sodium chloride, adenine, glucose and mannitol (SAGM) in comparison with traditional red cell concentrates due to removal of excess plasma [103,104].

Reactions to platelets are caused by leukocyte-derived cytokines and proinflammatory mediators that accumulate in the component during storage. Most blood services have implemented additive solution for BC-PC. The use of platelet additive solution which results in reduction of remaining plasma can lead to significant reduction of allergic

transfusion adverse events [105-107].

Transfusion related acute lung injury (TRALI) is caused by white blood cell antibodies in transfused blood components [108]. It occurs mainly after transfusion of fresh frozen plasma and PC. Pooled PCs contain less plasma from each donor, in particular if the pooled PCs are prepared with additive solution. However, in special cases, it has been demonstrated that even small plasma volumes can cause TRALI [109].

Leukocytes in the PCs can cause transfusion-associated graft-versus-host disease (TA-GVHD). TA-GVHD is mediated by the engraftment of allogeneic T-lymphocytes [110]. The risk of developing TA-GVHD depends on the viability and number of contaminating lymphocytes, the susceptibility of the recipient's immune system to their engraftment and the degree of HLA disparity between donor and recipient. Leukocyte filtration is not effective enough to produce the level of lymphocyte removal required to prevent TA-GVHD [111]. In this respect, a recipient of a pooled PC has a high risk of receiving a PC which contains plasma of a donor carrying WBC antibodies.

The use of universal leukoreduction, implemented in a growing number of countries, is a major decision to improve transfusion safety by drastically reducing the incidence of HLA immunization [112], and adverse reactions in patients [100,113].

Bacterial and viral contaminations

Some reports have demonstrated that buffy coat platelets have contamination rates similar to apheresis platelets but PRP method has higher contamination [114,115]. This phenomenon is presumably due to increased time for leukocyte-mediated bacterial killing provided by overnight hold of the whole blood which is an optional step in the process of buffy coat platelet production.

The theoretical argument of increased risk for transfusion-transmitted infections (TTI) due to a "pooling" of infectious agents in BC-PC may create a new challenge. It has been demonstrated that the use of apheresis PC leads to lower donor exposure of the recipient [116,117]. That means if platelets of four or five donations are pooled, the risk of infection is increased compared to a single unit. In the case of pooling there might be a chance that if one of the donors is infectious for hepatitis B, another donor contributing to the pooled PC product carries an amount of neutralizing antibodies. Due to the higher risk for TTI in first time donors [37,118,119], only repeat donations should be used for preparation of pooled BC-PC. Theoretically, higher leukoreduction in BC-PC relative to PRP-PC can enhance safety against TTI in cell-associated transmission of infections such as CMV, EBV, HIV, Toxoplasma gondii and similar infections. Therefore, it can be concluded that using modern whole blood processing techniques may prevent bacterial contamination [120].

Extended storage of buffy coat platelet concentrates

The most recent development in platelet component processing involves the use of platelet additive solutions (PAS) to dilute the BC before PC separation [121-124]. Use of PAS allows maximal plasma and platelet harvest if before PAS addition the BCs are pooled with a sterile tubing welder [125]. Since the first attempts to use platelet additive solutions, many improvements have been achieved, and although in vivo recovery of platelets is slightly decreased, many advantages are related to their use [126]. Among them, a significant reduction in adverse allergic reactions to transfusion is clearly demonstrated [106,107,127-129].

Buffy-coat processing allows for the use of PASs that reduces plasma-associated transfusion reactions and conserves plasma for transfusion or fractionation. Newer PASs, for example, SSP+ and Composol, can maintain PLT integrity and moderate metabolism similarly to plasma but offer consistently lower PLT recoveries and limited osmotic balance [130]. One recent study has shown that BC-PC stored in either plasma or 65% Plasmalyte meets FDA's post-storage viability criteria for 6 days [41]. Another study has indicated that rapid cooling of whole blood to room temperature is not required to meet FDA quantity and quality platelet standards. Eliminating the need to use cooling plates would represent a substantial cost-saving to blood centers [131].

Automation and standardization

The two production methods have differences that affect the operational efficiency of a production laboratory. For example, with the PRP method, there are more stringent limitations on the allowable production time that may limit the preparation of certain components such as platelets. With the buffy coat method, these production time

limits are less stringent thereby facilitating both laboratory workflow and increasing the ability to prepare components from the greatest proportion of whole blood collections. For the production laboratory, buffy coat platelets production method may require more overall effort than PRP method, but the finished product is generally leukoreduced with better quality. Overall, new technologies are coming that further improve the process control and increased use of automation in component production [132,133].

In addition, PRP–PC preparation is fully manual, and has at least one highly sensible step in term of platelet activation after the high speed centrifugation, while BC–PC can be produced with an automatic process with a high and reproducible platelet recovery [134].

Blood fractionation systems that include removal of the buffy-coat layer have evolved considerably in the past two decades, with a shift from manual extraction procedures to fully automated systems that allow standardized extraction and contribute to good laboratory practice in the preparation of blood components. The use of quality control systems in blood banks has made it necessary to adopt working methods that guarantee reproducible obtainment of the blood components; this in turn accommodates quality analyses of the products obtained on a routine basis, with careful control of the processing procedures involved [135].

Cost-effective benefits

The main topic of cost also comes into consideration when decisions are made. Unfortunately, there are no published comparisons of each blood component's costs from country to country determined by using the same criteria. For the manufacturer, BC-PC is a cost-effective method, due to the increased recovery of plasma and a 24-hour production window that permits all manufacturing to be done on the day after collection. Furthermore, BC pooled platelets reduce the cost of platelet therapy, because the BC-PC is pooled during production, it has lower overall leukoreduction costs than PRP-PC and can be used by both the blood transfusion services and the hospitals without further modification [136]. In addition, new technologies are being developed that further improve the process control in component production such as decreased RBC,

platelet, BC and plasma discard rates, improved labor productivity with better yields for platelets, plasma and RBCs [132,133].

To date, formal cost-effectiveness analyses on leukodepletion are scarce and are mainly derived from observational, retrospective data. However, the few studies that are available show a favorable economic profile for selected clinical indications. For instance, utilizing observational clinical data in an economic model, leukodepletion of platelets appears to be cost-saving when applied in adult acute myelogenous leukaemia [137].

Furthermore, leukodepletion of platelets in acute myelogenous leukemia and lymphoma patients and leukodepletion of whole blood in colorectal surgery have shown lower hospital costs compared to unfiltered blood products [138,139]. In coronary artery bypass graft surgery patients, leukodepletion of erythrocytes was cost-saving [140]. The Canadian Coordinating Office for Health Technology Assessment concluded that universal leukodepletion would not be cost-saving but that selective leukodepletion, that is, applying it to all patients who had an established indication for its use (such as frequently transfused patients), might be cost-saving [141].

In addition, use of neocyte therapy by using the Neocel® System that is a simple method and relatively low cost can benefit the majority of chronically transfused patients by reducing transfusional iron overload and related complications in BC-PC method 88. On the other hand, extension of the platelet shelf life by 2 to 3 days in BC-PC method can improve platelet inventory and efforts of donor recruitment tremendously, as well as the overall cost of this type of product to patients.

Finally, it is logically clear that lower risk of infections and adverse reactions in BC-PC relative to PRP-PC can improve safety public health and minimize the healthcare cost.

Summarizing the advantages and disadvantages

As mentioned above, some disagreements are observed in the results of the reports about BC-PC method versus PRP-PC method. For example, neither the HSR, nor the ESC showed sensitivity to time in storage [16,142] and the test results are significantly affected by the test diluents [143] which may reflect inconsistency among the protocols used by different laboratories. Other differences may be

related to the protocol of platelet preparation, pooling kit method or the chain method [144,145], type of additive solution [146-149], type of storage container [150-153], rapid cool down of whole blood after collection [154], type of cell separators [155,156] and the timing of BC preparation from either fresh or overnight-stored whole blood that influences metabolic activity, storage lesion and platelet count [145].

Incompatibility between in vivo and in vitro studies is another challenge for platelet products. It is accepted that the assessment of platelet quality is normally made in the first instance using in vitro laboratory assays. Unfortunately, there is no single laboratory test than can accurately predict the efficacy of a platelet transfusion [157]. Meanwhile, poor correlations between in vitro assays and in vivo survivability of PCs are sometimes seen in α-granule release [158], morphology score [159], P-selectin [160-162] and pH [163]. A possible explanation for this inconsistency is that platelet activation/degranulation is an independent process that sometimes, but not always, runs in parallel to the mechanism that leads to decreasing platelet viability. In the quest for an in vitro assay that can predict in vivo outcome, one must also consider that the platelet storage lesion appears to be somewhat reversible; platelets regain lost function after transfusion [164]. In addition, in vitro quality of platelets and the in vivo effectiveness of platelets depend on various factors like leukoreduction [165], storage temperature [166-169], the plastic material of the storage bag [162] gas exchange capabilities of the PLT storage container [153,170], platelet concentration in the storage container [171,172], and duration of storage [173,174], the type of anticoagulant used, the platelet concentration in the bag and the agitation[175].

These facts may also help to explain why poor correlations between in vitro assays and in vivo survivability or discrepancies in results are sometimes seen in the reports.

In acute transfusion reactions, it should also be considered that quality of the product in terms of residual WBCs, plasma content, storage period and patient factors may be more important than platelet product type.

In summary, the advantages of BC-PC relative to PRP-PC include: increase in leukoreduction of blood components, decrease in TRALI and TA-GVHD adverse reactions to blood components,

decrease in in-vitro platelet activation, possible extension of platelet storage beyond 7 days, better process control by semi-automated production equipment and more efficient use of staff, more cost-effectiveness due to increase in recovery of plasma for fractionation industry, reduction in microaggregation formation and its consequences in transfused patients, lower cost of platelet transfusion therapy, reduction in post-transfusion infections such as CMV, HIV, EBV, possible reduction in the incidence of bacterial contamination of blood components, increase in the removal rate of plasma in BC-PC that may reduce allergic transfusion adverse events and pathogen reduction, decrease in platelet alloimmunization and refractoriness, possible improvement of platelet yield, equal or better in vivo platelet recovery and survival, lower work load due to a 24-hour production window and standardization, lower leukocytes interaction and cytokine release, possible separation of blood components by differential centrifugation and possible improvement by new additive solutions, high applicability to pathogen reduction/inactivation systems, possible lower hematocrit levels in BC-PC, decrease in loss of red blood cells and possible preparation of therapeutic hemoglobin solutions (neocytes).

On the other hand BC-PC relative to PRP-PC may have some limitations such as: equal or lower platelet recovery, identical platelet survival and viability, lower quality of RBC in red cell units, increase in the number of residual WBCs in the 24-hour RBC units before leukodepletion step and possible lower quality of frozen plasma due to small decrease in factor VIII activity.

Above evidence show that BC-PC has a better quality than PRP-PC. This is due to these facts that most European countries have adopted this technique [10].

Conclusion

Decisions to convert from PRP-PC to BC-PC method in whole blood component production should be made. The benefits from increased platelet yield and quality, reduced bacterial contamination rates as well as cost-effectiveness compared to the PRP method might outweigh any transient difference in red cell parameters. It seems, in the process of converting, the prominent challenge is probably between the improvement

of the quality/safety of platelet and saving more plasma on one side, and the lower quality of red blood cells and somewhat frozen plasma units on the other side.

Furthermore, the products need regular re-assessment since new developments may have impact on the quality of various product types. From a risk management point of view it is advisable that a blood transfusion service should keeps both methods of preparation on hand. Further studies are recommended to assess the clinical significance of these two methods and in vivo results in terms of clinical efficacy and the viability of the stored platelets to patients.

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