

REVIEW

Buffy-coat-derived pooled platelet concentrates and apheresis platelet concentrates: which product type should be preferred?

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Vox Sanguinis

There is an ongoing debate whether platelet concentrates (PCs) prepared from either whole-blood donations or by plateletpheresis are superior. Usage of these two product types varies greatly between countries and individual institutions. Some use mainly apheresis PCs; others prefer pooled PCs which are produced from whole-blood donations.

This review summarizes the existing information on these product types. In the first part data on quality, efficacy and safety are reviewed. It is important to note that the issue cannot be answered just by comparing 'the' apheresis platelet concentrate versus 'the' pooled platelet concentrate. Other factors which determine the quality of a product, e.g. residual leukocyte count, plasma content, additive solution or storage period may be even more important. The focus of the debate should be shifted. It is much more needed to further improve the overall quality of PCs and to optimize treatment of thrombocytopenic patients than to concentrate on a single-edged view on just the preparation method.

In the second part of this review we compare the product types from the donor's point of view. If PCs which are equally safe and effective can be obtained by various methods, ethics and the safety of the healthy volunteer donor tips the scales.

The decision on the use of a particular product type should take into account all aspects of efficacy, side effects and availability of the product as well as the donor's perspective and the commitment to maximize the use of the valuable whole-blood donation.

Keywords: Adverse events, donor complications, platelet apheresis, Platelet concentrate, pooled platelet concentrates

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Introduction

Platelet transfusions play an important role in prevention or treatment of bleeding in patients with thrombocytopenia or severely impaired platelet function. Platelet concentrates (PCs) available for transfusion are prepared either from whole-blood donations or by platelet apheresis procedures. Both products are in widespread clinical use. For example

in Germany, about 40% of PC produced in the year 2007 were whole blood derived and 60% were produced by apheresis [1]. When comparing European Countries supposed to provide a similar transfusion service, the respective use of apheresis PCs and pooled PC is very heterogeneous [2]. In 2004, the use of pooled PCs ranged from 10% to 98% [3].

Two methods of preparing PCs from whole blood are in use. The predominant method in Europe is the buffy-coat (BC) method and in the United States the platelet rich plasma (PRP) method [4]. The two methods mainly differ in the centrifugation steps and have been described in detail in a recent publication in this Journal [5]. For production of pooled PCs from BC either the pooling kit method or the chain method can be used [5], also there are manual and

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automated methods of pooling [5–7]. Pooled platelets prepared by the BC method are usually stored in additive solution rather than in plasma making more plasma available for clinical use and reducing the plasma-associated transfusion reactions [8]. The type of additive solution influences integrity, metabolism, recovery and function of platelets [8–10]. The timing of preparation of BC-derived platelets from either fresh or overnight-stored whole blood influences metabolic activity, storage lesion and platelet count [11]. Several studies demonstrated that PCs produced from whole blood by the BC method after an overnight hold have laboratory characteristics suggestive of a higher quality than those concentrates produced by the PRP method [2,3,12].

As a result of the different preparation methods there is substantial variability of the products with regard to number of pooled donations, platelet content, residual leukocyte count, plasma content, type of additive solution and timing of the processing steps. There has been an ongoing debate whether one of these types of platelet products has clear advantages over the others. In this review, we will summarize the existing evidence, in particular comparing PCs from apheresis donation with PCs from whole-blood donation. Given the differences between PCs produced by the PRP method and the BC method in terms of preparation, *in vitro* function and adverse events [2,3,12], we try to discriminate between the different types of whole blood-derived PCs.

Quality control data: content of platelets and other components

With platelet apheresis it is possible to collect enough from a single donor to constitute at least one transfusion dose. It is possible to collect up to more than 8×10^{11} platelets per apheresis session [13]. Usually these are divided into two therapeutic units of about 3×10^{11} platelets [13,14]. In new, still experimental approaches triple apheresis with production of three therapeutic units is attempted [14,15]. A recent study demonstrated that high-yield plateletpheresis donation can correlate with reduced transfusion efficacy and that in-vivo studies are necessary to assess the quality of the products [16].

To obtain a therapeutic dose of platelets from whole-blood donations requires pooling of the BC from four to six donations [5].

In our hands, the platelet content as well as the number of residual white blood cells and erythrocytes is not different between a therapeutic unit of pooled PCs which are prepared with the chain method from BCs or apheresis PCs which are mainly split products of double apheresis (Fig. 1). Also others found similar platelet content and mean platelet volume comparing BC-derived and apheresis PCs [17,18] or similar platelet content in BC-derived PCs [19,20] and similar number of leukocytes [21,22].

Quality control data: *in vitro* and *in vivo* studies

Methods of platelet preparation may alter the functional characteristics, recovery and survival of platelets following transfusion. Using a paired study, *in vivo* and *in vitro* characteristics of apheresis platelets and single-donor whole blood platelets prepared by the PRP methods were compared after storage for 5 days in similar plastic containers. There was no significant difference in circulating recovery between $^{111}\text{Indium}$ labelled platelets prepared by the two methods. Hypotonic shock recovery was significantly better in apheresis than whole blood platelets (57.0% and 32.4%, respectively), whilst aggregation to ADP at 3.2 and 32 μM was significantly higher in whole blood PRP platelets than in apheresis platelets (17.0% and 45.2% versus 7.8% and 32.9%, respectively). There was no significant difference between the two platelet preparations for platelet concentration, pH, aggregation with the calcium ionophore A23187 or collagen plus epinephrine, or ATP content or release. Release of β -thromboglobulin was lower in apheresis platelets [23].

Another well designed study compared platelet recovery and survival for apheresis PCs and whole blood derived PCs (by PRP method) using autologous radiolabelled platelets. Both preparations were leukodepleted [24]. These were given as autologous transfusions to volunteer donors using a crossover design where each volunteer donated in random order both apheresis PCs and whole blood for PRP preparation. Five day stored apheresis PCs had 18.8% better recovery, and longer survival than PRP PCs. Stored apheresis platelets had lower p-selectin expression and higher morphology scores than stored PRP platelets [24]. However, given the substantial differences between whole blood derived PCs produced by either BC or PRP method, these results may not apply to all types of PC preparation.

Activation marker CD62P is not different between apheresis and pooled BC PCs [18,25]. However, the percentage of platelets with exposure of phosphatidylserine as a marker of platelet injury was found to be higher on day 5 of storage in apheresis PCs compared to BC PCs [18]. A significant correlation was found between phosphatidylserine exposure and microvesiculation [18].

In a study comparing *in vitro* variables of PCs produced by apheresis or the BC method the percentage of platelets with depolarized mitochondrial membrane potential as a marker of deterioration of mitochondrial integrity increased significantly in BC PCs but not in apheresis PCs [25]. However, no significant change was detected in the platelets ability to consume oxygen in both preparations and no difference in viability [25].

In a study of variability between donors various parameters were analysed, including the platelet plug formation,

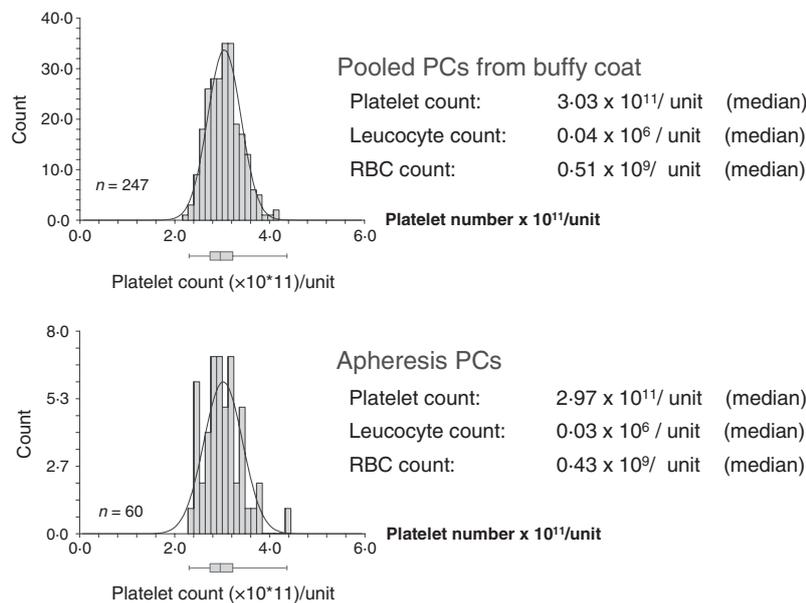


Fig. 1 Platelet content (per therapeutic unit) in apheresis PCs and pooled, buffy-coat-derived PCs produced by the chain method (pool of 4 buffy coats) (quality control data; German Red Cross Blood Service Baden-Württemberg – Hessen).

the prevalence of impaired thromboxane formation, and the effects of the density in alpha-2 integrin polymorphism and density [26]. The collagen-epinephrine induced closure time showed a great inter-subject variability in platelet donors and was higher than in healthy controls. One-fifth of donors had abnormal closure time values. Decreased serum thromboxane B2 levels were found in 9% of all donors, compatible with surreptitious intake of cyclooxygenase inhibitors or with an aspirin-like defect. Thus, a substantial proportion of platelet donors present with prolonged closure times. The prolonged collagen-epinephrine induced closure time was associated with a short interval between donations [26].

In summary, the various *in vitro* and *in vivo* studies did not demonstrate that one of the products (apheresis PCs versus pooled PCs) was consistently better than the other for the parameters tested. Given the inter-donor variability in platelet function, *in vitro* pooling before transfusion leads to a reduction of the variations between the products.

Efficacy

Posttransfusion platelet increment is an important surrogate marker to assess the efficacy of platelet transfusions. Several studies directly compared corrected count increments (CCI) after transfusion of apheresis or whole blood-derived platelets [27–33]. In a systematic comparison on the basis of raw data from some of these studies [27–31], Heddle *et al.* found a higher 1-h CCI with apheresis PC compared with all whole blood-derived PCs when

PRP and BC-derived PCs were combined. However, when whole blood-derived PCs were stratified into pooled PCs prepared by either BC or PRP method, a significant difference remained between apheresis PCs and PRP pooled PCs, but there was no significant difference between apheresis PCs and BC-derived pooled PCs. As with the 1-h CCI, there was a significant difference between apheresis PCs and PRP pooled PC for the 18- to 24-h CCI, but apheresis PCs and BC-derived pooled PCs were again not different [34].

The ‘Trial to Reduce Alloimmunization to Platelets (TRAP) Study Group’ evaluated patient- and product-related characteristics that influence posttransfusion platelet response and interval between platelet transfusions. Platelet factors that were associated with improved platelet response were giving AB0-compatible platelets and platelets stored less than 48 h [35]. Similarly, platelet factors that were associated with significantly longer time to next transfusion were storage of 48 h or less and increasing platelet dose. In contrast, type of platelet product (apheresis PCs, leukodepleted pooled PCs), AB0 incompatibility or γ -irradiation had no influence on the transfusion intervals [35].

Patient factors that improved platelet responses were splenectomy and increasing patient age. In contrast, at least two prior pregnancies, male gender, splenomegaly, bleeding, fever, increasing height and weight, lymphocytotoxic antibody positivity, an increasing number of platelet transfusions, or receiving heparin or amphotericin were associated with decreased post-transfusion platelet responses [35]. Similarly, significantly shorter

transfusion intervals were associated with at least two pregnancies, male gender, dissemination intravascular coagulation, positivity for lymphocytotoxic antibodies, bleeding, fever, infection, palpable spleen, increasing number of transfusions, treatment with amphotericin or heparin [35].

The decline of CCI associated with storage of the product for longer than 48 h was confirmed by others [36,37]. However, as the comparison by several investigators demonstrated this is a general phenomenon observed with both apheresis PCs and pooled whole blood-derived PCs [28,32,37].

In a study on AML patients ($n = 33$) the efficacy of apheresis PCs and PRP PCs given prophylactic in the first 100 days after myeloablative stem cell transplantation was compared [33]. Single-donor apheresis PCs produced better platelet counts, but apheresis PCs and pooled PCs were equally effective in preventing haemorrhage [33].

In the study of Heim *et al.*, patient factors affecting the platelet transfusion results in terms of CCI were age, gender, treatment category and number of previous transfusions [36]. Age showed a biphasic pattern with higher CCI for young patients (< 10 years) and for patients older than 40 years. Allogeneic stem cell transplant recipients had a significantly lower transfusion efficacy, whereas patients treated with antithymocyte globulin had better CCIs compared with patients treated with chemotherapy alone [36]. Inverardi *et al.* demonstrated that patients with detrimental factors (in this study defined as fever, bacteremia, haemorrhage, coagulopathy, progenitor cell transplantation, toxic medications) had poor response to both apheresis PCs and pooled BC-derived PCs and response to both products recovered after resolution of the detrimental factors [37]. An advantage of apheresis PCs in terms of higher CCI was observed in alloimmunized patients, but only if patients were transfused with human leucocyte antigen (HLA)-compatible platelets [37].

In summary, so far there is no convincing evidence that efficacy in terms of CCI or interval to next transfusion is superior with either apheresis PCs or pooled PCs in non-alloimmunized recipients. Patients with refractoriness due to HLA- and or human platelet antigen (HPA)-antibodies require transfusion of apheresis PCs from matched donors. The studies equivocally demonstrate the great impact of patient-related factors on platelet increments, transfusion intervals and platelet refractoriness. Unfortunately, the information on outcomes such as incidence and severity of bleeding or time to next transfusion is scanty. Without information on such endpoints no final conclusion on superiority of one of the products in terms of efficacy can be drawn. Further studies comparing in particular BC-derived pooled PC with apheresis PC are needed.

Safety

Febrile non-hemolytic transfusion reaction

Febrile non-hemolytic transfusion (FNHTR) reactions are the most common adverse reaction to platelet transfusions [38]. Reactions to platelets are caused by leukocyte-derived cytokines that accumulate in the component during storage. Therefore, only products with similar leukocyte content should be compared. In a randomized comparison, no difference in the acute reactions were reported comparing pre-storage leukoreduced apheresis PCs and pre-storage leukoreduced whole blood-derived PCs prepared by the PRP method (13.3 vs. 11.4%) [31]. In a prospective randomized study from the UK, the probability of the occurrence of a FNHTR following transfusion of PCs showed a significant decrease for apheresis PCs and pooled PCs produced by the BC method (3.1% and 3.8% respectively) when compared with pooled PCs produced by the PRP method (17.1%) [27]. Also the TRAP Study Group reported that apheresis PCs did not independently influence reaction rates. Reaction rates were low with both apheresis PCs and filtered, pooled random-donor PCs which were prepared with the PRP method (1.6% vs. 1.8%, resp) and significantly higher with pooled random-donor PCs which were not leukodepleted (2.5%) [40]. Use of platelet additive solution which results in reduction of remaining plasma from individual donors leads to significant reduction of allergic transfusion adverse events [22,41,42]. Most Blood Services have implemented additive solution for BC-derived PCs. Also preparation of apheresis PCs can be adapted to use additive solution. However, additive solution so far is not used to the same extent for apheresis PCs as it is already the case for BC-derived PCs. But even if additive solution is used for apheresis PCs the remaining plasma volume is about 60–120 ml from one donor. In contrast, the plasma in BC-derived PCs originates from four to five donors. The volume of plasma from the individual donor is only about 15–25 ml. In a systematic review, Heddle *et al.* found no difference in acute reactions when leukoreduced whole blood-derived pooled PCs (PRP and BC method) and apheresis PCs were compared [34]. Thus, quality of the product in terms of residual leukocytes, plasma content or storage period and also patient factors seem to be more important for acute transfusion reactions than platelet product type – at least as long as apheresis PCs and pooled BC-derived PCs are compared.

Bacterial and viral contamination

A reservation against pooled PCs came from the theoretical argument of increased risk for transfusion-transmitted infections (TTI) due to a 'pooling' of infectious agents. It

has been argued that use of apheresis PCs leads to lower donor exposure of the recipient [43,44].

However, the current tests for detection of human immunodeficiency virus (HIV), hepatitis B and C virus (HBV, HCV) have reduced the infectious risk for these viruses to a very low level in the range below $1:4 \times 10^6$ for HIV and below $1:10^7$ for HCV [45–47]. Of course, if platelets of four or five donations are pooled, the risk of infection is increased compared to a single unit. However, does this translate into increased risk for the recipient when comparing apheresis PC and pooled, whole blood-derived PCs? As counterbalance to a 'pooling' of infectious agents, one must take into account a 'distribution' effect by apheresis PCs. If one of the whole-blood donors contributing to a therapeutic PC unit would be infected with a TTI, this would result in exactly one infectious therapeutic PC unit. If an apheresis donor who is a regular donor or who donates by double-/triple-plateletpheresis procedure is infected, this can result in several infectious therapeutic PC units [48,49]. The majority of apheresis PC units nowadays are prepared by a double- or triple-apheresis procedure. As a consequence up to three therapeutic units per apheresis procedure can be produced [43]. According to the guidelines which are in place in many countries the maximum frequency of donation is higher for plateletpheresis compared with whole-blood donation. This translates into higher average number of donations and shorter interval between donations. The probability of several donations in the therapeutic window is higher in plateletpheresis donors and might lead to donation of more than one infectious units in the window period [50]. Given the higher risk for transfusion-transmitted infections in first-time donors [46,51,52], only repeat donations should be used for preparation of pooled PCs. In case of pooling there might be a change that if one of the donors is infectious for Hepatitis B, another donor contributing to the pooled PC product carries a sufficient amount of neutralizing antibodies. Asymptomatic donors with persistent hepatitis B infection who are HBsAg-negative and pool PCR-negative might escape detection if no test for anti-HBc is performed [53,54].

It is difficult to assess the relative impact of all these aspects on the final outcome. There might be no general answer to this. It depends on prevalence of the infection in the donor population, the detection limit and diagnostic window of the infection, the average donation frequency, the number of pooled units in whole blood-derived PCs, the number of therapeutic units per apheresis and the donation intervals. However, it must be emphasized that a bunch of factors play a role and it is not that simple to assume that the risk of transmission of an infectious disease is just multiplied by factor 4 or 5 in case of pooling platelets from four or five whole-blood donations. Mathematical models on the risk of transfusion-transmitted infections have been

published [43,55]. However, so far, no epidemiological study or clinical trial have demonstrated different risk of viral infections transmitted by pooled PCs compared to apheresis PCs.

Bacterial contamination of PCs is a longstanding problem in transfusion medicine. Prevalence data vary considerably from one study to the next [56–59]. The incidence of reported clinically relevant reactions to contaminated platelet products is much lower [60–62]. Nevertheless, bacterial contamination is now considered as the most frequent clinical relevant infectious risk of platelet transfusion [56]. It was suggested to use generally apheresis PCs instead of whole blood-derived pooled concentrates since higher bacterial contamination rates or higher incidence of septic platelet transfusion reactions in pooled products has been reported when comparing sequential time periods [60].

Theoretically, one would assume that pooling of four or five BCs would increase the risk of bacterial contamination by the same factor. However, using whole-blood donations which were spiked with bacteria it has been shown that the preparation procedure for random BC-derived pooled PC can reduce titres by several log [63]. In a prospective study comparing contamination rates in more than 15 000 apheresis PCs and more than 37 000 pooled PCs by aerobic and anaerobic cultures we found a significantly lower rate of potentially positive pooled PCs compared to apheresis PCs and equal rate of confirmed positive apheresis and pooled PCs [64]. Other studies arrived at similar results [39,65]. When comparing published data on bacterial contamination of platelet products one must take into account the strategies which have been implemented in the recent years to reduce the risk of bacterial contamination: guidelines excluding donors with risk of bacteraemia are in place; skin disinfection has been improved by implementation of skin disinfectant standard operation protocols with repeated application and defined minimum resident time of disinfectant prior to venipuncture; the diversion of the first 30–40 ml has been introduced in many centres. It has been demonstrated that all these measures can be effective for reduction of bacterial contamination of blood products [66–69]. Pathogen inactivation or reduction systems that are applicable to platelets (Intercept™, Mirasol™) will further reduce the risk of transfusion reactions due to bacterial contamination [70,71]. Some Blood Services already started to use pathogen-inactivated PCs on a regular basis [72,73]. It has been demonstrated that most septic transfusion reactions occurred with PCs at day 5 after collection [74]. Therefore, shortening of the shelf-life of PCs can reduce death due to septicaemia because of undetected bacterial contamination.

Thus, already now with PCs reflecting current standards of donor selection, collection and preparation the risk of bacterial contamination does not warrant universal

preference of APC. Further improvements such as introduction of pathogen inactivation systems for PCs or reduced shelf-life of platelets will further reduce the risk of septic transfusion reactions in all types of PCs.

Alloimmunization and platelet refractoriness

Several studies addressed whether transfusing only apheresis PCs can prevent alloimmunization as measured by lymphocytotoxic antibodies and refractoriness as defined by poor posttransfusion increments [29,30,75]. In a meta-analysis combining studies that used non-leukoreduced products, the overall relative risk for allosensitization was not significantly different between apheresis PCs and pooled whole blood-derived PCs [34].

In the TRAP trial patients who were receiving induction chemotherapy for acute myeloid leukaemia were randomly assigned to receive one of four types of platelets transfusions: unmodified, pooled PCs from random donors; filtered, pooled PCs from random donors; ultraviolet B-irradiated, pooled PCs from random donors; or filtered platelets obtained by apheresis from single random donors. All patients received transfusions of filtered, leukocyte-reduced red cells. Of 530 patients with no alloantibodies at base line, 13% of those in the non-leukodepleted, pooled PC group produced lymphocytotoxic antibodies and their thrombocytopenia became refractory to platelet transfusions, as compared with 3% in the leukodepleted pooled PC group, 5% in the UVB PC group, and 4% in the leukodepleted apheresis AP group. The rate of alloimmunization was significantly lower in all groups as compared with non-leukodepleted pooled PCs. However, there were no significant differences amongst the other groups [30]. Of the product-related factors, γ -irradiation was associated with a significant increase in platelet refractory rates, whereas refractory rates were the same regardless of the type of platelets transfused [35].

Overall there is no evidence that apheresis PCs and pooled random-donor PCs differ in the rate of alloimmunization as long as the products are leukodepleted [30,34,35].

Transfusion-related acute lung injury

Immune-TRALI is due to white blood cell antibodies in transfused blood components [76]. It occurs mainly after transfusion of fresh-frozen plasma and PCs. Pooled PCs contain less plasma from each individual donor, in particular if the pooled PCs are prepared with additive solution. Then the residual plasma from each donor is less than 25 ml. However, in anecdotal cases, it has been demonstrated that even small plasma volumes can cause TRALI [77]. On the other hand, a recipient of a pooled PC has a higher risk of receiving a PC which contains plasma of a

donor carrying WBC antibodies. TRALI has been reported both after transfusion of pooled whole blood-derived PCs as well after apheresis PCs. In a retrospective analysis of American Red Cross Surveillance data apheresis PCs were 7.9-fold more likely to be implicated in TRALI than RBCs. No significant difference was seen between the estimated rate of probable TRALI with RBCs and whole blood PCs [78]. In a prospective cohort study, consecutive transfused critically ill patients were closely observed for development of TRALI. Cases received more PC transfusions than controls, but the use of apheresis PCs or pooled PCs did not differ between cases and controls [79]. These limited data available so far do not allow a clear conclusion on an advantage of single-donor apheresis concentrates versus pooled PCs.

Donor perspective

Whole-blood donation and plateletpheresis share many of the donor complications such as complications related to needle insertion (mainly vessel and nerve injuries) and general reactions [vasovagal reactions (VVR)]. However, there are also specific complications of the apheresis donation due to the collection method and the frequency of donation (Table 1).

Several studies on donor complications in whole-blood donors and apheresis donors showed variable results (Table 2).

Acute reactions: whole-blood donation and apheresis donation

Both apheresis and whole-blood donors can experience adverse reactions like weakness, pallor, sweating, nausea

Table 1 Specific risks and problems of apheresis donations

Extracorporeal circulation (extracorporeal volume)
Platelets: modulation of glycoprotein expression; activation
Increased loss of platelets → thrombocytopenia: acute/chronic?
Citrate with potential risk of citrate-related toxicity
Hypocalcaemia may cause
Vascular smooth muscle relaxation
-Depressed myocardial function
-Arrhythmia
-Chronic metabolic (late) effects of citrate : bone demineralization
Exposure to foreign substances with risk of allergic or toxic reactions (ethylene oxide; DEHP)
Increased loss of lymphocytes? → immune deficiency?
Risk of air embolism
Separator-/Set-related problems
Logistic aspects
Additional resources required: staff, equipment, room
Time-consuming for the donor

Table 2 Comparison of risk of apheresis vs. whole-blood donation (Frequency of donor complications (per 10⁵ donations))

Reactions	Whole blood	Apheresis	Reference
Moderate reaction	377.5	116.2	Wiltbank & Giordano, 2007 [84]
Severe reaction	93.5	32.2	
All adverse reactions	1761	1073	Franchini <i>et al.</i> , 2002
VVR (moderate/severe)	125	46	
Local injury	381	358	
Citrate toxicity	–	77	
Major reactions	74	52	Eder <i>et al.</i> , 2008 [121]
Outside medical care	32	29	
Citrate reactions		1221	
All reactions	3489	5775	
Moderate reactions	226		Shehata <i>et al.</i> , 2004
Severe reactions	46		
Venipuncture related reactions		1117	McLeod <i>et al.</i> , 1998 [122]
Non-venipuncture related reactions		1020	
Venipuncture related		530	Despotis <i>et al.</i> , 1999 [111]
Hemodynamic/citrate related		350	
Very severe complication (requiring hospitalization)		35	
Very severe complication (requiring hospitalization)	0.2		Popovsky <i>et al.</i> , 1995 [123]
All adverse reactions	83		Schrezenmeier <i>et al.</i> , 2008 [124]
VVR (all)	47	931	
VVR (severe) Citrate	15	0	
Reactions	–	931	

VVR, vasovagal reactions.

and fainting. This can occur during or after collection. In whole-blood donors, the incidence rate of these vasovagal reactions (VVR) is higher in younger donors, females and at first time of donation [80,81]. In contrast, the age dependency is weak in apheresis donors. One study reported a particularly high incidence rate in women apheresis donors over 45 years of age [82]. The VVR increases with the number of cycles [82]. Both in whole-blood donors [83] and apheresis donors [82] the circulatory blood volume is a strong predictor of VVR.

In recent studies, the rate of moderate and severe reactions was estimated at 0.38% and 0.09% after whole-blood donation and 0.12% and 0.03% after plateletpheresis [84].

Risk of thrombocytopenia and lymphocytopenia after apheresis donation

Several studies addressed the long-term effects of regular apheresis donation on platelet and lymphocyte count. Early reports suggested a lymphocyte depletion [85–92], decline in CD4 + or CD8 + count [88,90,91], decline in B-cell counts [87] and immunoglobulin levels [89,90,92], decline in response to stimulatory molecules (e.g., alloantigens) [90]. However, modern devices which have been designed to produce leucocyte depleted components do not remove a large number of lymphocytes. A recent study did not observe adverse effects of frequent apheresis donations on

white blood cell counts [93]. However, also with modern separators and up-to-date software a modest, but significant decline of lymphocytes associated with number of plateletpheresis donations and number of products donated can occur [15].

Lazarus *et al.* reported that regular plateletpheresis donors develop significant and sustained decreases in platelet count [94]. The frequency of donation correlated directly with decrease in platelet count. In this study, a mean decrease of $40 \times 10^9/l$ from baseline occurred in the frequent-donor subgroup [94]. In other studies, only small decrement of platelets were observed which were considered as clinically insignificant and no consistent relationship between the changes in platelet counts and the number of products donated per year was observed [95–98]. Short interdonation intervals were associated with statistically decreases in platelet counts [98]. The study by Richa *et al.* reported an increase of platelets associated with the number of products donated [15]. Some devices exceed the platelet target substantially which can result in high platelet loss for donors [99].

In a study comparing donors undergoing plateletpheresis for the first time to those donating platelets every other week for more than 18 months, the median levels of reticulated platelets were significantly lower in frequent donors than in new donors. The authors concluded that repeat platelet donation might lead to a relative exhaustion of

thrombopoiesis, as evidenced by the low levels of reticulated platelets exhibited by repeat donors [100].

So far, there is no evidence for clinical immunomodulation as a consequence of the changes in these surrogate markers. Also clinical significant thrombocytopenia due to plateletpheresis is unusual – at least when guidelines on frequency of donations and pre-donation platelet counts are established and followed. However, on the other hand, we must ask whether sufficient long-term monitoring is in place to ensure detection of late adverse events.

Exposure to citrate: metabolic and endocrine effects of apheresis donation

Citrate is used as anticoagulation in platelet apheresis. Mean plasma citrate concentration in the donor progressively increase during plateletpheresis and reach up to a median of 1.6 mM [101]. This leads to a decrease in ionized calcium. In a study by Bolan *et al.*, an average fall in ionized calcium of 33% from baseline was reported [102]. This can lead to symptoms of citrate toxicity such as paresthesias (predominantly perioral and acral), light-headedness, tremor and shivering. Hypocalcaemia may cause vascular smooth muscle relaxation, depressed myocardial function, arrhythmia and chronic metabolic (late) effects of citrate (e.g. bone demineralization).

Prophylactic oral calcium was associated with only modest improvements in these citrate-induced symptoms [103]. In addition, plateletpheresis induced increase in parathyroid hormone, osteocalcin and 1,25-dihydroxyvitamin D, increased urinary excretion of Ca, Mg, K and Na. Serum alkaline phosphatase levels declined during apheresis [104]. Oral Ca supplementation exerted a clinically modest effect on these variables [104]. Therefore, there is concern that infusion of citrate anticoagulant solutions which accompany plateletpheresis procedures impair donor calcium balance and bone density despite calcium administration [104]. A study reported on increased markers of bone metabolism in plateletpheresis donors and radiological signs of osteopenia in about 1/3 of frequent plateletpheresis donors. Similar changes were not detected in a control group of sporadic donors [105].

Citrate also binds magnesium. Citrate administration during plateletpheresis decreases ionized magnesium by about 30%. This can cause symptoms such as muscle weakness, muscle spasms and impaired myocardial contractility [106]. Hypomagnesemia and concomitant influence the parathormone response during apheresis [106].

Single-donor plateletpheresis results in a temporary increase in serum thrombopoietin levels. This may be – together with other haematopoietic cytokines – part of a compensatory haematologic response required to replenish the loss of platelets by apheresis [107]. Whether this

response is different from whole-blood donation remains to be determined. Thrombopoietin induces P-selection expression, subsequent platelet/leucocyte interactions and increased adhesion under flow and decreases rolling [108,109]. Whether temporary cytokine responses and their functional consequences are relevant and whether these responses are different in apheresis donors and whole-blood donors remains to be studied.

Exposure to citrate: arrhythmogenic effects of apheresis donation

Steady-state plasma ionized calcium levels inversely correlate with the QT interval. Prolongation of the QTc interval during plateletpheresis is a general finding. It can be considered as a sensitive marker of citrate toxicity at the myocardial tissue level. Citrate infusion has been associated with drop in blood pressure, decreased cardiac output [110,111] and cardiac arrest [112]. Hypotensive adverse events are often preceded by citrate-induced hypocalcaemia symptoms. Citrate-related symptoms are the most significant independent predictor of hypotension [111].

Exposure to foreign substances: allergic reactions and potential toxic effects of apheresis donation

Due to the extracorporeal circulation donors can be exposed to foreign substances released from the disposable apheresis set. Allergic reactions to ethylene oxide used to sterilize the sets have been reported, predominantly in repeat apheresis donors who developed IgE antibodies to ethylene oxide [113,114]. Reactions in donors sensitized to ethylene oxide ranged from mild allergic symptoms to severe anaphylactic reaction.

Di(2-ethylhexyl)phthalate (DEHP) is a plasticizer that is contained in most PVC devices, including apheresis disposables. Considerable amounts of DEHP are released from the disposable set during apheresis [115–117]. Median increases of up to 232% of serum DEHP compared with baseline levels have been reported [117]. Metabolite excretions were found to be significantly higher for plateletpheresis compared with plasmapheresis and controls [115]. Continuous-flow plateletpheresis led to significantly higher excretions than discontinuous-flow plateletpheresis. Mean DEHP doses for plateletpheresis were close to or exceeded the reference dose of the US EPA and tolerable daily intake value of the EU on the day of the apheresis [115].

Other apheresis-related events, logistic aspects and cost

Finally, set- and separator-related problems such as leakage of the system and flow problems have to be taken into

account. These sometime require early termination of apheresis.

Also the risk of air embolism cannot be absolutely excluded. However, the residual risk now is very low since all modern apheresis devices contain detectors for air in the extravascular circulation which stop the procedure immediately.

Furthermore, scar formation due to frequent venipuncture might occur, which could facilitate bacterial contamination during subsequent donations.

Also the effort is in average higher for the plateletpheresis donor. He has to travel to the apheresis centre, whereas in most areas, the majority of whole-blood donations are collected by mobile teams. Since most of the plateletpheresis donations aim to collect two units the duration of the donation itself is much longer [3].

Preparation of apheresis PCs requires more additional resources in terms of staff, equipment and room which can be attributed to plateletpheresis. This is reflected in higher cost of apheresis PCs. However, it is difficult to provide exact figures on the difference because the accounting system, the attribution of costs and the pricing policy differs substantially between institutions [22,118,119]. In one study on cost-effectiveness it was concluded that the use of apheresis PCs as opposed to pooled random donor platelets may not be a cost-effective method of reducing donor exposure in an adult patient population [44].

Critical appraisal of adverse events of whole-blood donation and apheresis donation

The risk of donor complications of whole blood as well as apheresis donation is low but not negligible. Comparison of event rates of donor complication after whole blood and apheresis arrive at controversial conclusions, mainly due to a substantial heterogeneity of data. This heterogeneity is due to differences in definition of events, donor selection, collection volume and changes over time with the advent of new technologies for blood collection. The profile of adverse events differs substantially between apheresis and whole-blood donors. In addition to the puncture-related adverse events which apply to all types of donation, apheresis donors may experience unique complications due to extracorporeal circulation, metabolic and arrhythmogenic consequences of citrate exposure and exposure to foreign substances.

The donor complications should not only be assessed *per donation* but also *per therapeutic unit(s)* obtained by the donation. One should also take into account *the purpose* of the donation. The apheresis is solely undertaken to generate the PCs and the whole risk of the apheresis has to be attributed to the PCs. The whole-blood donation is necessary to meet the demand for RBC transfusions. If one would use

exclusively apheresis PCs and would completely abstain from production of whole blood-derived PCs, we would still need the same number of whole-blood donations to ensure adequate RBC supply, i.e. this would not change the risk of whole-blood donation. Only a small proportion of whole-blood donations are used to also make pooled PCs. As an example, in Germany, only about 41 units of pooled PCs have been produced per 1000 donations. In the year 2007, more than 4.7 millions of whole-blood donations were collected. The overall number of PC produced in the year 2007 in Germany was about 480 000 (287 000 apheresis and 193 000 pooled PCs) [1]. Thus, even if all the apheresis PCs would be substituted by BC-derived PCs there would be still an excess number of whole-blood donations based on the current demand for pooled PCs.

Therefore, from the donor's perspective the additional risk of preparation of a pooled PC unit from the whole-blood donation which would have been collected anyhow is zero! If we do require plateletpheresis to provide a unique benefit to the recipient, e.g. for HLA-/HPA-matched PCs, the risk of donations seems appropriate. If safety and efficacy of the two components, either apheresis PCs or whole blood-derived PCs, are equivalent, the difference in donor complications is a strong argument to prefer whole blood-derived PCs.

How does our Blood Service manage supply with platelet concentrates in daily practice ?

As outlined above the existing evidence suggests equivalence of apheresis PCs and pooled BC PC-derived PCs in terms of quality, safety and efficacy. In this situation, we prefer pooled BC-derived PCs as routine supply for non-allosensitized patients. This is based on availability of BCs for PC production in our Blood Service collecting more than 750 000 donations annually. Even if pooled PCs are preferentially prepared from BC of donors with blood group A and O and even if we exclude first-time donors from preparation of pooled PC more than 530 000 BCs per year are available for production of pooled PCs. The annual demand is in the order of 60 000 units. The commitment to our donors prompts us to use this resource and to avoid putting donors at additional risk unless justified for specific reasons. We use apheresis PCs for allosensitized patients or if additional PCs with specific characteristics are required, e.g. PCs from donors who are blood group O, RhD negative and CMV-negative, in particular in periods with lower than normal numbers of whole-blood donations, e.g. holiday seasons. As a consequence the majority of PCs are supplied as pooled BC-derived PCs. As an example, Fig. 2 shows how the proportion of pooled versus apheresis PCs in a large hospital including haematology/oncology service and paediatric and adult stem cell transplantation

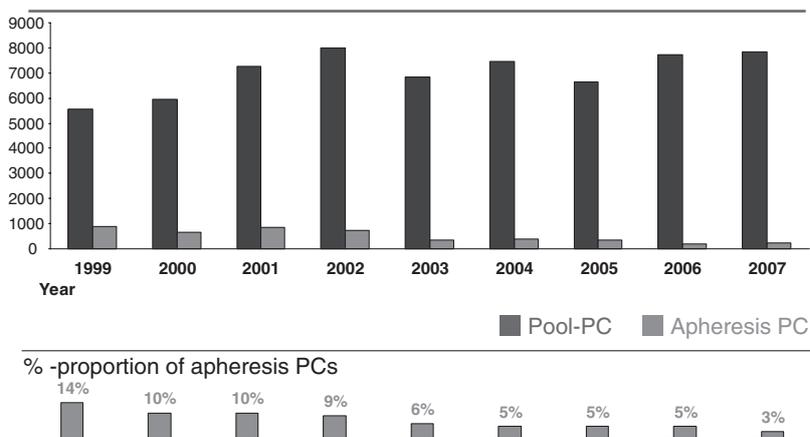


Fig. 2 Absolute number and relative proportion of apheresis PCs and pooled buffy-coat-derived PCs transfused in a university hospital in the period 1997–2008.

programme developed over the last 10 years. The relative proportion of apheresis PCs declined, most likely due decreasing medical need for apheresis PCs after implementation of universal leukodepletion in Germany in October 2001 and is now in the order of only about 3% of all PC units transfused.

Conclusion

There is a bunch of data, some are conflicting, on quality, safety and efficacy of PCs prepared by different methods

(Table 3). In summary, there is some advantage of pooled platelets prepared by the BC method over the PRP PCs. However, in comparison between apheresis PCs and pooled BC-derived PCs the data suggest equivalence of the products in non-allosensitized recipients. A clear advantage of apheresis PCs can only be demonstrated in allosensitized patients with HLA- and or HPA-antibodies who receive antigen-compatible apheresis PCs. On this basis it was recommended to base the product choice mainly on availability and medical indication [120]. The comparative studies were mainly based on surrogate parameters. We are

Table 3 Summary of advantages and disadvantages of PCs produced by plateletpheresis as compared to whole blood-derived pooled PCs (using the buffy-coat method)

		BC Pool-PC (leuko-depleted buffy-coat-derived in additive solution)	Apheresis PC
Donor	Donor complications	no	Possible
Product	Platelet content	++	++ (+) ^a
	Residual leukocytes	Low	Low
	Plasma content*	Low (<100%)	High
Adverse events	Transfusion reactions		No difference
	Allosensitization/Refractoriness		No difference
	Bacterial contamination		No difference
Efficacy	Platelet increment		
	Random		No difference ^b (+)
	Allosensitized patients (HLA/HPA-antibodies)		+++
	Bleeding		No sufficient data
	Time to next transfusion		[no difference] ^c
Cost		++	+++

^aHigher platelet content could be achieved by plateletpheresis compared to pooled PCs. However, most Blood Services produce split products by double or triple apheresis. On the level of the therapeutic unit the platelet content is not different.

^bEfficacy very much dependent on clinical condition of recipient.

^cOnly limited data available.

missing sufficient comparative data on prevention or treatment of bleeding or the interval between transfusions. Thus, from the point of clinical relevance current evidence none of the products proofed superior.

From the donor's point of view, the additional risk of producing pooled PCs from the whole-blood donation is zero. On the other hand, there are specific adverse events of plateletpheresis which is undertaken solely to generate apheresis PCs and put the donor at risk. The frequency of adverse events is very low, but not zero. The research on donor complications so far focussed on acute reactions. Long-term effects, in particular taking into account late consequences of metabolic effects, are less investigated. Therefore, to be on the safe side from the donor's perspective we are in favour of using the abundance of platelets available from whole-blood donation.

On the basis of currently available data, we prefer pooled PCs derived from whole-blood donation and prepared by the BC method unless a specific clinical condition such as neonatal immune thrombocytopenia or platelet refractoriness due to alloantibodies requires transfusion of matched PCs (Table 3). However, further studies are needed, in particular prospective trials comparing the product types for clinically relevant endpoints. When deciding about the PC supply strategy, every Blood Service has to take into consideration its own specific requirements and conditions, e.g. number of available whole-blood donations; number of refractory patients, number of immunocompromised patients requiring CMV-negative products. The decision must balance donor safety and optimal use of the blood donors' gift with an optimal management of the patients. Furthermore the comparison between the product types needs regular re-assessment since new developments, e.g. pathogen inactivation, also have impact on the assessment of the various product types. From a risk management point of view it is advisable that a Blood Service has both methods of preparation on hand.

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