Efficacy and Adverse Events of Platelet Transfusion – Product-Specific Differences

Peter Hellstern

Institut für Hämostaseologie und Transfusionsmedizin, Klinikum der Stadt Ludwigshafen, Germany

Key Words

Platelet transfusion · Apheresis platelet concentrates · Pooled platelet concentrates · Efficacy · Adverse events · Logistics

Summary

Two preparations are available for platelet transfusion: single-donor apheresis platelet concentrates (APC) and pooled platelet concentrates (PPC) prepared from 4–6 whole blood units. Clear advantages of APC over PPC are a markedly reduced donor exposure of recipients, and easier logistics when attempting a complete supply with ABO-identical and Rh-compatible platelet concentrates. Regulations should aim at complete ABO-identical platelet transfusions because major and minor ABO-incompatible platelet transfusions are probably associated with significantly increased morbidity and mortality. The main advantage of PPC is lower costs. Preparation of PPC is however inevitably accompanied by substantial wastage of plasma and red cells. Only major supraregional blood transfusion centers can guarantee full-coverage supply with ABO-identical and Rh-compatible PPC. Whether APC are more effective than PPC and associated with fewer septic platelet transfusion reactions as shown in some but not all studies, has to be examined in future prospective controlled trials.

Schlüsselwörter

Thrombozytentransfusion · Thrombozytapherese-konzentrate · Gepoolte Thrombozytenkonzentrate · Wirksamkeit · Verträglichkeit · Logistik

Zusammenfassung

Für die Thrombozytentransfusion stehen von Einzelspendern gewonnene Thrombozytapheresekonzentrate (TTK) und gepoolte Thrombozytenkonzentrate (GTK) aus jeweils 4 bis 6 Vollblutspenden zur Verfügung. Sichere Vorteile von TTK sind die deutlich geringere Spenderexposition der Empfänger und eine einfachere Logistik, wenn eine lückenlose Versorgung mit AB0-gleichen und Rh-kompatiblen TK angestrebt wird. Da die AB0-ungleiche Thrombozytentransfusion höchstwahrscheinlich mit einer deutlich höheren Morbidität und Mortalität einhergeht, ist die AB0-gleiche Transfusion anzustreben. Der wesentliche Vorteil von GTK liegt in den geringeren Herstellungskosten. Die Herstellung von GTK geht jedoch mit einem erheblichen Verlust an Plasma und Erythrozyten einher. Nur große, überregionale Blutspendedienste können eine lückenlose Versorgung mit AB0-gleichen und Rh-kompatiblen GTK gewährleisten. Ob TTK wirksamer sind als GTK und ob der Einsatz von TTK mit niedrigeren Raten an bakterieller Sepsis einhergeht, wie einige Arbeitsgruppen zeigten, muss in künftigen prospektiven, kontrollierten Studien geprüft werden.

Introduction

Platelet concentrates can be prepared either by plateletpheresis (apheresis platelet concentrates, APC) from single donors or by pooling 4–6 platelet-rich plasma or buffy coat units (pooled platelet concentrates, PPC) from whole blood units. A recent International Forum that reviewed the PLT transfusion

policies of 16 countries revealed substantial differences in the use of these platelet preparations [1]. Centers that use APC exclusively or that are using them increasingly maintain that alloimmunization occurs less frequently after transfusion of this type of platelet concentrate compared with PPC, with the added benefit that patients are exposed to the blood of fewer donors. In addition, apheresis platelets facilitate supply of al-

loimmunized patients with compatible platelets. Experts who combine the use of APC and PPC argue that PPC are less costly, and that the availability of apheresis donors is limited. This review focuses on differences between these 2 types of platelet concentrates in regard to clinical efficacy and adverse events, and on conclusions that should be drawn from these data with regard to platelet transfusion strategies.

Clinical Success of Platelet Transfusion

Several small studies have compared non-white blood cell (WBC)-reduced PPC with APC, noting no significant difference between APC and PPC in corrected count increments (CCI), recovery, or platelet survival. All of these studies however were either deficient in statistical power or suffered from flawed design [2–7]. Another prospective randomized trial examining posttransfusion platelet recovery and CCI of WBC-reduced PPC and WBC-reduced APC in 115 patients noted a significantly increased success rate with APC after adjusting for platelet age [8]. The authors observed CCI values of $\geq 4.5 \times 10^9$ platelets/l in 35% for the WBC-reduced PPC and in 53% for APC ($p < 0.0001$). The same study group performed a prospective crossover trial examining in vivo recovery and survival of autologous WBC-reduced apheresis platelets and autologous leukoreduced platelets prepared from whole blood, both preparations stored for 5 days, in 22 healthy volunteers [9]. The apheresis platelets had a 18.8% better recovery and survived 32.9% longer than did platelets prepared from whole blood. Finally, a small retrospective analysis of 105 PPC and 41 APC transfusions in 33 patients suffering from acute myeloid leukemia or myelodysplastic syndrome who had received allogeneic hematopoietic stem cell transplants demonstrated a significantly greater CCI after APC ($p = 0.0001$) [10]. However, the difference in refractoriness rates between the groups was not statistically significant due to the low number of observations (APC, 17%; PPC, 30%; $p = 0.1$).

Donor Exposure

One advantage of APC is that donor exposure to patients is reduced. At first sight, the use of PPC, which is prepared from 4 whole blood donations, would seem to increase donor exposure 4-fold compared to APC transfusion. Donor exposure would be 8-fold if a patient required 2 therapeutic doses, which could conceivably be obtained from a single individual in the course of 1 plateletpheresis session. This difference in donor exposure between PPC and APC is already sufficient to wreck the increase in blood product safety gained through the introduction of nucleic acid amplification testing for HIV and HCV [11]. In Germany, about 150,000 PPC are produced annually from 620,000 whole blood units donated by 485,000 individuals [12]. Assuming that platelet transfusion policies aim-

ing at minimal donor exposure might approach average annual donation frequencies of 20 APC per person, these 150,000 platelet concentrates could theoretically be obtained from a mere 7,500 donors, and total donor exposure might as a result be reduced by more than 60-fold. Others deny that donor exposure is reduced by using APC since plateletpheresis donors are allowed to donate more frequently than whole blood donors and therefore – if infectious – might donate several times during the window period for the infectious agent, transmitting the agent to several recipients [13]. However, this scenario can to a large extent be avoided by establishing a minimal donation interval of 2 weeks, since the diagnostic window period for HCV and HIV has been almost completely closed subsequent to the introduction of minipool PCR testing after virus enrichment [14]. A risk assessment conducted by the Economics, Statistics and Operational Research Department (ESOR) of the English Department of Health has shown a reduced risk of transmission of variant Creutzfeldt-Jakob disease (vCJD) by transfusion when single-donor platelets are compared with PPC [1]. Replacing PPC with APC completely would also conserve about 37,000 l of whole blood plasma in Germany alone. About 100 ml of red cells are wasted per 4 units of whole blood in the course of manufacturing PPC, adding up to 80,000 red cell concentrates per year.

ABO and Rh Compatibility

Several findings suggest that ABO-identical platelets should be used for transfusion wherever possible. Because A and B antigens express on platelet surfaces in subjects with corresponding blood groups, transfusing ABO incompatible platelets results in a substantial decrease in posttransfusion recovery and earlier onset of refractoriness [15–26]. The transfusion of group A and AB platelets to group O patients may reduce 1-hour posttransfusion platelet increment by up to 90% [15]. ABO-specific clinical refractoriness is frequently accompanied by an acute increase in isohemagglutinin titers [27, 28]. Reduced platelet recoveries may also occur after ABO minor-incompatible platelet transfusions [18, 19, 29]. These observations have been ascribed to immune complexes composed of donor A or B antibodies and soluble A or B substances in the blood of the recipients. These immune complexes may bind to complement or Fc receptors on platelets, leading to accelerated immune clearance [18, 19]. Early studies using non-leukodepleted platelet concentrates have shown that ABO-incompatible platelets can encourage HLA alloimmunization and the formation of platelet-specific antibodies [27, 30]. In the case of patients with acute myeloid leukemia or myelodysplastic syndrome who received either major or minor ABO-mismatched allogeneic bone marrow transplants, one study group attributed the increased rate of morbidity due to multiple organ failure or infection to platelet transfusions containing ABO-incompatible plasma [31, 32]. The risk of

veno-occlusive disease in children treated with high-dose chemotherapy and hematopoietic stem cell transplantation for neuroblastoma or brain tumors has been found to be significantly associated with the transfusion of platelet concentrates containing ABO-incompatible plasma [33]. A retrospective study observed multiple ABO-mismatched platelet transfusions to be associated with unfavorable outcomes in cardiac surgery [34]. A second retrospective analysis in patients who had had cardiac surgery was not however able to confirm these findings [35]. Nevertheless, concern about ABO-incompatible platelet transfusions will remain until dispelled by results from prospective controlled trials.

Severe hemolysis has been observed after transfusion of out-of-group platelet concentrates; particularly blood group O platelet concentrates to non-O patients [22, 25, 36, 37]. This can occur not only after transfusion of APC but also after PPC [25, 36]. As hemolysis might be delayed and unrecognized clinically, underreporting may be a serious challenge [37]. Although the risk of anti-D formation after RhD-incompatible platelet transfusions appears to be low [38–40], alloimmunization may occur even in immunocompromised recipients [41–43].

All these findings suggest that platelets should be transfused ABO-identically, and that RhD-negative children and women of childbearing age should receive RhD-negative platelet units only whenever possible. In clinical practice however the use of PPC hampers the implementation of this platelet transfusion policy. Assuming a frequency of blood group A, RhD-negative of 6% in the German population, a series of at least 130 whole blood donations per day would be required to produce 2 group A RhD-negative PPC from 8 whole blood donations. Daily production would have to be no less than 3,400 whole blood units to supply 1 group AB RhD-negative patient with 2 anti-CMV-negative ABO-identical and RhD-compatible PPC. In contrast, these 2 platelet units can be obtained from 1 plateletpheresis session. These calculations explain why only major supraregional blood transfusion centers can guarantee full-coverage supply with ABO-identical and RhD-compatible PPC. But it is just these centers however that frequently fail to provide hospitals with compatible platelets without unacceptable delay.

Non-Immune Causes of Platelet Refractoriness

The Trial to Reduce Alloimmunization to Platelets (TRAP) examined the outcomes of 6,379 platelet transfusions given to 533 patients. It found reduced platelet refractoriness rates to be associated with transfusing filtered apheresis platelets [23]. This agrees with recent studies suggesting higher success rates after transfusion of APC compared with PPC [8, 9]. However, prospective controlled trials are needed to find out whether there are differences in clinical efficacy between leukodepleted PPC and APC or not.

Bacterial Contamination

Septic platelet transfusion reactions are supposed to result from platelet concentrates contaminated by donor skin flora or won from donors with asymptomatic bacteremia. Since the production of 1 APC involves only 1 venipuncture, but at least 4 venipunctures are needed to get 1 PPC from whole blood units, it would seem obvious that PPC carry the greater risk of transmitting bacterial infections to recipients. One retrospective study has suggested a substantial decrease in septic platelet transfusion reactions after increasing the frequency of APC use from 51.7 to 99.4% of all platelet transfusions [44]. This was however not confirmed by a more recent prospective multicenter trial comparing PPC and APC, which did not reveal any differences in bacterial contamination between both types of platelet units [45]. In the latter study, the initial 30–40 ml of apheresis and whole blood collections were diverted to a pouch. This pre-donation sampling obviously eliminated possible differences in bacterial contamination between PPC and APC.

Further Aspects

Alloimmunized patients require HLA and/or platelet-specific antibody-matched APC. The platelet count in APC can be adjusted more precisely and more flexibly than in PPC. If platelet function assays were available that would accurately predict the quality and clinical efficacy of platelet concentrates before the donation, these could be applied much more easily for APC than for PPC. Substituting PPC with APC conserves plasma and red cells obtained from whole blood donations.

Conclusions

Aside from the fact that APC are – perhaps – more expensive than PPC and the minor risk of severe adverse events involved in plateletpheresis, all aspects of platelet transfusion are in favor of APC. If future prospective controlled trials can demonstrate that APC is clinically more efficacious, replacing of PPC with APC would require fewer platelet concentrates. Using APC instead of PPC reduces patient donor exposure substantially. Relatively few regular plateletpheresis donors are required to supply patients with all blood group constellations. In view of the severe adverse events that can result from ABO-incompatible platelet transfusions, policies prescribing the use of ABO-incompatible platelet concentrates to avoid wastage should be prohibited. Replacing of PPC with APC would save substantial amounts of plasma and red cells obtained from whole blood. Unlike PPC, APC are biopharmaceutical preparations since platelet count can be adjusted precisely, and platelet quality can additionally be evaluated by predonation platelet function tests.

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