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The Role of Plasma and Platelet Transfusion in Patient Blood Management – A Narrative Review

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ABSTRACT

Patient blood management (PBM) has been defined as the timely application of evidence-based medical and surgical concepts designed to maintain hemoglobin concentration, optimize hemostasis, and minimize blood loss in an effort to improve patient outcome. Primarily PBM focused on the avoidance of inappropriate red blood cell transfusion. However, inappropriate plasma and platelet transfusion seem to be at least as harmful as inappropriate red blood cell transfusion. Accordingly, the indication to transfuse "yellow blood products" should be considered carefully, too, and recent studies showed that at least most prophylactic or preemptive transfusion of plasma and platelets must be considered as inappropriate and potentially harmful. Here, transfusion-associated circulatory overload (TACO), transfusion-related lung injury (TRALI), transfusion-related immunomodulation (TRIM) and nosocomial infections are important issues related to transfusion of plasma-rich blood products and associated with increased morbidity and mortality. Therefore, this systematic review of the literature shall provide an overview about the risk-benefit ratio of plasma and platelet transfusion and shall increase the awareness regarding potential risks of inappropriate plasma and platelet transfusion under specific consideration of patients with end-stage liver disease and critically ill patients. In that context, bleeding management algorithms guided by viscoelastic testing (VET) can be helpful to implement a safe -, restrictive -, clinical- and cost-effective approach. Furthermore, coagulation factor concentrates, and hemostatic drugs can be integrated effectively and safely in this concept of VET-guided PBM.

Keywords: Plasma Transfusion; Platelet Transfusion; Patient Blood Management; Transfusion Associated Circulatory Overload; Patient Outcome; Patient Safety; Transfusion-Related Lung Injury; Transfusion-Related Immunomodulation; Hospital-Acquired Infections

Abbreviations: ESLD: End-Stage-Liver-Disease; SHT: Standard Hemostasis Test; VET: Viscoelastic Test; HIT: Heparine-Induced Thrombocytopenia; TTP: Thrombotic Thrombocytopenic Purpura; DIC: Disseminated Intravascular Coagulopathy; TACO: Transfusion-Associated Circulation Overload; TRALI: Transfusion-Related Acute Lung Injury; RBC: Red Blood Cells; ARDS: Adult Respiratory Distress Syndrome; INR: International Normalized Ratio; FDA: Food and Drug Administration; UK: United Kingdom; RCT: Randomized Controlled Trial; OR: Odds Ratio; SOFA: Sequential Organ Failure Assessment

Introduction

Patient blood management (PBM) has been defined as the timely application of evidence-based medical and surgical concepts designed to maintain hemoglobin concentration, optimize hemostasis, and minimize blood loss to improve patient outcome. Primarily PBM focused on the avoidance of inappropriate red blood cell transfusion [1]. Several randomized controlled trials (RCTs) and meta-analyses demonstrated that a restrictive red blood cell (RBC) transfusion strategy is as least as effective and safe as a liberal RBC transfusion strategy [2,3]. Notably, a restrictive RBC transfusion strategy has been shown to be superior to liberal transfusion in patients with gastrointestinal bleeding [4]. Here, inappropriate plasma and platelet transfusion might contribute to bleeding by increasing portal vein pressure in patients with cirrhosis [5]. Accordingly, inappropriate plasma and platelet transfusion seem to be at least as harmful as inappropriate red blood cell transfusion. Therefore, the indication to transfuse "yellow blood products" should be considered carefully, too, and recent studies showed that at least most prophylactic or preemptive plasma and platelets transfusion must be considered as inappropriate and potentially harmful. Here, transfusion-associated circulatory overload (TACO), transfusion-related lung injury (TRALI), transfusion-related immunomodulation (TRIM) and nosocomial infections are important issues related to transfusion of plasma-rich blood products and associated with increased morbidity and mortality [6]. Therefore, this systematic review of the literature shall provide an overview about the risk-benefit ratio of plasma and platelet transfusion and shall increase the awareness regarding potential risks of inappropriate plasma and platelet transfusion under specific consideration of patients with end-stage liver disease and critically ill patients. Platelets play an important role in primary hemostasis and inflammation. Reports from patients with bone marrow hypoplasia recommend a minimum of 7.1/nl platelets to maintain vascular integrity [7]. In nonsurgical patients, spontaneous bleeding episodes have been reported with a platelet count ≤ 5/nl [8,9]. However, the platelet count does not correlate well with function. A platelet count of 50/nl has been reported to provide better primary hemostasis in patients with ESLD compared with healthy volunteers [10]. Accordingly, the hemostatic function of platelets should be assessed by point-of-care devices, such as Multiplate or ROTEM platelet [11]. Platelet transfusion is associated with the highest sepsis rate among all blood products [12]. In liver transplant patients, platelet transfusion is associated with decreased long-term survival [13,14]. Bleeding due to plasmatic coagulopathy should be ruled out with VET before platelet transfusion is considered. Desmopressin and/or tranexamic acid may be adequate in some cases of platelet dysfunction [15,16], and platelet transfusion may be considered if bleeding cannot be controlled by other therapeutic options. Platelet transfusion is contraindicated in heparin-induced thrombocytopenia (HIT) or thrombotic thrombocytopenic purpura (TTP), and it should be considered very carefully in disseminated intravascular coagulation (DIC) associated with bleeding [17]. However, most recommendations for platelet transfusion are based on weak evidence [18,19].

Search Strategy

We performed a systematic review of the literature with the PubMed search terms ((((prophylactic FFP transfusion[Title/Abstract]) AND ((outcome[Title/Abstract] OR outcomes[Title/Abstract] OR harm[Title/Abstract] OR adverse events[Title/Abstract] OR complications[Title/Abstract] OR mortality[Title/Abstract] OR survival[Title/Abstract] OR TRALI[Title/Abstract])))) in October, 2020. Sixteen keynote publications are listed in Table 1. Some papers are highlighted in the following paragraphs. Similar query was used for platelet transfusions. A literature search was conducted regarding platelet transfusion in PubMed as we did for FFP. The search terms were ((((prophylactic platelet transfusion [Title/Abstract]) AND ((outcome[Title/Abstract] OR outcomes[Title/Abstract] OR harm[Title/Abstract] OR adverse events[Title/Abstract] OR complications[Title/Abstract] OR mortality[Title/Abstract] OR survival[Title/Abstract] OR TRALI[Title/Abstract])))), (October 20, 2020). Twenty-five keynote publications are listed in Table 2. Some papers are highlighted in the following paragraphs.

Adverse Events Due to FFP and Platelet Transfusion

In critically ill patients, transfusion of fresh-frozen plasma (FFP) is associated with a three-fold increase in nosocomial infections [20]. Modulation of the immune system with the deregulation of regulatory T-cells has been found as the underlying mechanism. TRALI remains the leading cause of transfusion-associated death in the US, with an incidence rate of 1.4–3.0% among the adult population undergoing surgery [21]. TACO is another severe complication caused by transfusion, with a reported incidence of 3.0–5.5% in the US [22]. According to the UK SHOT report for 2013, 12 out of 22 patients with TACO (54.4%) died [23]. Moreover, plasma transfusion in trauma patients who did not require massive transfusion (< 10 U packed red blood cells [RBCs] within 12 hours of hospital admission) was associated with a 12-fold increase in acute respiratory distress syndrome (ARDS), a six-fold increase in multiple organ dysfunction syndrome, and a four-fold increase in pneumonia and sepsis [24]. ABO-compatible but non-identical plasma transfusion is associated with increased morbidity and mortality compared with ABO-identical plasma transfusion [25]. Although a blood transfusion may be lifesaving in some cases of severe bleeding, strategies to avoid unnecessary or inappropriate plasma transfusion and platelet transfusion should be addressed to avoid transfusion-related complications, deaths, and increased costs.

Table 1: Keynote publications about FFP transfusion.

Author/Year	Clinical Setting, Key Results
FFP Effectiveness	
Kozek-Langenecker/2011 [71]	The weight of evidence does not support the clinical effectiveness of FFP for surgical or massive trauma.
Bjursten/2013 [72]	Transfusion of FFP was associated with increased mortality in aortic surgery (HR = 1.041; p<0.001).
Bjursten/2013 [73]	FFP transfusion in aorto-coronary bypass surgery decreased long-term survival (HR = 1.06, p < 0.001).
Huber/2019 [74]	Cochrane Database Syst Rev. Prophylactic use of FFP can neither support nor oppose it because of limited RCT evidence.
FFP vs. Prothrombin Complex Concentrate (PCC) in Warfarin-related Bleeding	
Karaca/2014 [75]	Patients with active upper gastrointestinal bleeding who are under warfarin For 17 of the 20 patients who received PCC (85%), the INR level at the second hour was below 2.1, while none of the patients who received FFP had an INR level were at or below 2.1; the reversal with PCC was faster, and none of the PCC receiving patients was active bleeding during endoscopy compared with 7 patients in the FFP group with Forrest 1a bleeding.
Marshall/2016 [76]	Almost 20% of patients who received FFP for warfarin reversal developed pulmonary complications, primarily TACO, and this risk increased with > 3 units of FFP (OR 2.49; 95% CI [1.21–5.13]).
Chai-Adiasaksopha/2016 [77]	Meta-analysis of 5 RCT and 8 observational studies: compared with FFP, the use of PCC for warfarin reversal was associated with a significant reduction in all-cause mortality, more rapid INR reduction, and less volume overload without an increased risk of thromboembolic events.
Cost-Effectiveness Analysis	
Guest/2010 [78]	Model analysis of UK National Health Service: PCC appeared to be a more cost-effective treatment than FFP for the emergency reversal of warfarin.
TRALI (Transfusion-related Acute Lung Injury (ALI))	
Khan/2007 [79]	FFP transfusion OR 2.14; 95% CI [1.24–3.75] for ALI
Vlaar/2013 [80]	Narrative Review: Excluding female donors of products with high plasma volume, resulting in a decrease of roughly two-thirds in incidence of ALI.
Schmickl/2015 [81]	Meta-analysis 13 cohort studies, 1 RCT: Risk for ALI and mortality in plasma recipients exposed to male plasma compared with plasma from female: risk ratio (RR): 0.27; 95% CI [0.2–0.38] for mortality RR: 0.89; 95% CI [0.8–1.0].
Morita 2014 [82]	Cohort: liver transplant recipients, n = 632; TRALI incidence: 1.4 %, Mortality 11%
Peters / 2019 [83]	Secondary analysis of two cohort studies designed to identify TRALI risk factors by matching TRALI patients to transfused controls. Conclusion: Donor age, donor sex, and donor blood type are unrelated to TRALI
TRIM (Transfusion-related Immunmodulation)	
Sarani/2008 [84]	Transfusion of fresh frozen plasma is associated with an increased risk of infection in critically ill patients. Association between transfusion of fresh frozen plasma and ventilator-associated pneumonia with shock (relative risk 5.42, 2.73–10.74); for bloodstream infection with shock (relative risk 3.35, 1.69–6.64).
Mica/ 2016 [85]	Trauma patients. N = 2033: The transfusion of FFP led to a more severe systemic inflammatory response syndrome (SIRS), to a higher infection rate (48% vs 28%; P<.001), and to a higher sepsis rate (29% vs 13%; P<.001).
Ming/2020 [86]	Cardiac surgery: N = 8238 patients Transfusion of any blood type was associated with higher rates of mortality (2.0% vs 0.18%; P < .01) and infection (13.3% vs 4.8%; P < .01). Each of the 3 blood products was independently associated with an increase in mortality per unit transfused (red blood cells, odds ratio 1.18, 95% confidence interval [CI], 1.14–1.22; fresh frozen plasma, odds ratio 1.24, 95% CI, 1.18–1.30; platelets, odds ratio 1.12, 95% CI, 1.07–1.18). Transfusing 3 units of the 3 blood products was associated with a dose-dependent increase in the incidence of mortality (odds ratio 1.88, 95% CI, 1.70–2.08) and infection (odds ratio 1.50, 95% CI, 1.43–1.57).

Table 2: Keynote publications about platelet transfusion.

Author, Date	Clinical Setting, Key Results
Preoperative or Preprocedural Thrombocytopenia	
Estcourt, et al. [64]	Insufficient evidence to recommend the administration of preprocedural prophylactic platelet transfusions.
Schmidt, et al. [87]	Preprocedural platelet transfusion is associated with an increased risk of thrombosis (5%) and 30 day mortality (16%). Most deaths were because of infection, sepsis, or organ failure, and none were because of bleeding or thrombosis.
Warner, et al. [88]	Platelet transfusion was associated with increased rates of intensive care unit admission (OR [95% CI], 1.57 [1.07–2.32]; p = 0.022).
Warner, et al. [89]	Patients receiving platelet transfusions had higher rates of intensive care unit admission (OR [95% CI], 1.95 [1.10–3.46]; p = 0.0224) and longer hospital lengths of stay (estimate [95% bootstrap CI], 7.2 [0.8–13.9] days; p = 0.0006) in propensity-adjusted analyses.
Duffy, et al. [90]	Mortality in the platelet transfused group was 43% versus 5% in the nonplatelet-transfused group.
Cirrhosis, Gastrointestinal Bleeding, and Liver Transplantation	
Kumar, et al. [91]	RCT; Significantly lower use of blood components (FFP, PLTs, and cryoprecipitate) in the TEG group compared with the standard group. Failure to control bleeding, failure to prevent rebleeds, and same mortality between both groups.
Zheng, et al. [14]	Patients who received apheresis platelet transfusion had a lower 90-day cumulative survival (78.9% vs. 94.2%, P = 0.009).
Nacoti, et al. [92]	Red blood cell and platelet transfusions are independent risk factors for postoperative complications in the first year after pediatric liver transplantation.
Zakko, et al. [65]	Platelet transfusions in patients with gastrointestinal bleeding who were taking antiplatelet agents without thrombocytopenia did not reduce rebleeding but were associated with higher mortality.
Chin, et al. [93]	Lower graft and overall survival were observed in patients receiving intraoperative platelet transfusion.
Fayed, et al. [94]	Recipients of LTx were divided into two groups: group I (GI) (n = 76) platelet count (PC) ≥ 50×10^9/l and group II (GII) PC < 50×10^9/l (n = 76). Platelets were transfused following a thromboelastometry protocol and clinical signs of diffuse bleeding. Each group was further subdivided according to platelet transfusion (PTx) into (GI NPTx and GII NPTx) with no platelet transfusion (NPTx) and (GI PTx and GII PTx) received PTx. 75% avoided PTx in GII. In GII, PC increased after the start of surgery. Recovery of platelets was quicker, and the duration of mechanical ventilation and ICU stay was shorter in NPTx patients, regardless the base line PC.
Pereboom, et al. [13]	Patient and graft survival were significantly reduced in patients who received platelet transfusions compared with those who did not (74% vs 92%, and 69% vs 85%, respectively, at 1 year; P < 0.001).
Critically Il and Burns	
Kaserer, et al. [95]	Platelet transfusion was independently associated with systemic inflammatory response syndrome (OR, 4.5; 95% CI, 1.3–15.5; p = 0.018) and mortality (OR, 5.8; 95% CI, 2.1–16.0; p = 0.001).
Warner, et al. [66]	Patients receiving prophylactic platelet transfusions had significantly higher red blood cell transfusion rates (OR, 7.5 95% CI, 5.9–9.5; P < 0.001), fewer ICU-free days (mean [standard deviation] 20.8 [9.1] vs. 22.7 [8.3] days; P = 0.004), fewer hospital-free days (13.0 [9.7] vs. 15.8 [9.4] days; P < 0.001), and less improvement in sequential organ failure assessment scores (mean decrease of 0.2 [3.6] vs. 1.8 [3.3]; P < .001).
Traumatic Brain Injury (TBI) and Intracerebral Hemorrhage (ICH)	
Furay, et al. [15]	57 patients with TBI (Desmopressin, n = 23; PLT, n = 34). Before treatment, both groups had similar ADP inhibition as measured by thromboelastography (ADP, 86% vs. 89%, p = 0.34). After treatment, both the DDAVP and platelet transfusion groups had similar corrections of platelet ADP inhibition (p = 0.28). Conclusion: DDAVP may be an alternative to platelet transfusions to correct platelet dysfunction in TBI patients.
Thorn, et al. [96]	Systematic review: Impact of platelet transfusion in TBI patients receiving antiplatelet treatment. This systematic review demonstrates a lack of clear evidence of the mortality benefit of platelet transfusion in TBI patients while on antiplatelet therapy. The pooled RR indicated a higher mortality with the use of platelet transfusion (RR, 1.50; 95% CI, 0.93–2.42; I2, 43%; prediction interval, 0.49–4.58).
Leukemia, Chemotherapy, and Stem Cell Transplantation	
Estcourt, et al. [70]	Cochrane Database Syst Rev. Hematological disorders: because of myelosuppressive chemotherapy or hematopoietic stem cell transplantation, low-quality evidence that a standard trigger level is associated with a decreased number of transfusion episodes when compared with a higher trigger level (20 x 10^9/L or 30 x 10^9/L).
Dengue Fever	
Lee, et al. [97]	Platelet transfusion in absence of bleeding in adult Dengue with a platelet count of <20,000/mm^3 did not reduce bleeding or expedite platelet recovery. There was potential harm by slowing recovery of platelet count to >50,000/mm^3 and increasing the length of hospitalization.
Prashantha, et al. [98]	Among Jehovah's Witnesses, platelet counts recovered to >50,000 in 2.57 days (mean) as compared with those who received prophylactic platelet transfusion, who recovered in 4.43 days (P value < 0.0001). They also had significantly fewer numbers of days of hospitalization (3.68 days vs. 5.13 days, P value < 0.0001).

Neonates	
Fustolo-Gunnink, et al., [99]	Post hoc multivariate logistic regression model in the PlaNet-2 data, which supports the threshold for platelet transfusion of 25 x 10^9/L. The 25 × 10^9/L threshold was associated with absolute risk reduction in all risk groups, varying from 4.9% in the lowest risk group to 12.3% in the highest risk group. These results suggest that a 25 × 10^9/L prophylactic platelet-count threshold can be adopted in all preterm neonates, irrespective of predicted baseline outcome risk.
Waller, et al., [100]	Neonatal hemorrhaging is often co-observed with thrombocytopenia, the causal relationship seems controversial, and accurate assessment of platelet function can be performed by flow cytometry. Flow cytometric measurement of platelet function identified clinically different neonatal groups and may eventually contribute to assessment of neonates requiring platelet transfusion.
Curley, et al., [99]	RCT; Platelet transfusions are commonly used to prevent bleeding in preterm infants with thrombocytopenia. Preterm infants with severe thrombocytopenia who received platelet transfusions at a platelet-count threshold of 50/nl had a significantly higher rate of death or major bleeding within 28 days after randomization than those who received platelet transfusions at a platelet-count threshold of 25/nl.
Du Pont-Thibodeau, et al. [101]	Pediatric ICU, platelets are mainly prophylactically transfused. 60/842 (7,1%) received at least 1 unit of platelets. Platelet transfusions were associated with the development of multiple organ dysfunction syndrome and increased mortality.
Sparger, et al., [102]	Among the 972 very-low-birth-weight infants, 231 received 1,002 platelet transfusions. Transfusions were mainly done as prophylaxis. The severity of thrombocytopenia did not correlate with the risk for intraventricular hemorrhage, and platelet transfusions did not reduce this risk.
Baharoglu, et al. [69]	RCT, acute spontaneous primary intracerebral hemorrhage in people taking antiplatelet therapy. 2 groups, with and without platelet transfusion: The odds of death or dependence at 3 months were higher in the platelet transfusion group (OR, 2.05; p=0·0114).

Fresh Frozen Plasma Transfusion

In most hospitals, FFP transfusion is still the most used hemostatic intervention to prevent or treat bleeding due to complex coagulation disorders. However, there is a lack of evidence based on prospective, randomized control trials (RCTs) supporting this approach [26]. Recommendations in national and international guidelines on the use of plasma and platelet transfusions are based on weak evidence [27,28]. FFP transfusion for massive bleeding following trauma is common practice in the United States (US) [29], however, favorable outcome data from RCTs are still lacking. Pathologic standard coagulation tests (SCTs) in end-stage liver disease (ESLD) may be misinterpreted as a high bleeding risk. Accordingly, prophylactic FFP transfusion prior to invasive procedures should be strictly avoided. Recent [5,30] prospective studies using viscoelastic testing (VET) demonstrated decreased transfusion requirements in patients with liver cirrhosis [31,32]. Therefore, bleeding management algorithms guided by viscoelastic testing (VET) can be helpful to implement a safe and restrictive as well as clinical- and cost-effective approach [33]. Rare bleeding issues due to congenital factor V or factor XI deficiency may still require FFP transfusion since there are no factor V and factor XI factor concentrates available. FFP must be transfused at a dose of at least 15-20 ml FFP/kg body weight to achieve clinical effectiveness. Single doses below 600 ml FFP are hemostatically inadequate in adults [19]. FFP remains less effective than coagulation factor concentrates for correcting a coagulopathy [34]. TRALI is a severe and life-threatening complication, most often related to plasma transfusion. Banerjee, et al. [35] reported on a patient with bile duct obstruction by a tumor and prolonged international normalized ratio (INR: 1.8). Vitamin K and three! units of FFP were transfused to improve hemostasis. The patient developed severe ARDS related to the FFP transfusion soon after transfusion. Other causes of ARDS could be ruled out. This case describes the typical clinical course of TRALI due to FFP transfusion. In 2003, TRALI emerged as the leading cause of transfusion-related mortality, as reported by the US Food and Drug Administration (FDA) [36]. TRALI is characterized by acute hypoxemia and noncardiac lung edema, occurring within 6 h after transfusion [37]. Although most patients recover within three days, TRALI remains associated with a mortality rate between 5% and 25% [38,39].

Several recently published studies [40,41] demonstrated that patients with cholangiocellular or hepatocellular carcinoma are prone to thrombosis although standard coagulation tests indicated hypocoagulability. In contrast, clot amplitudes in the thromboelastometric assay FIBTEM could discriminate between patients who develop cancer-associated thrombosis or not [42]. Hence, the decision to transfuse FFP should be very restrictive. Indeed, a systematic review [43] including 57 randomized control trials (RCTs) raised serious concerns about the effectiveness of FFP transfusion. Prophylactic/preemptive plasma transfusion is still common practice in patients with ESLD or critically ill patients, based on the assumption that it may correct mild coagulopathy and prevent bleeding. A UK national survey [44] reported on 4,969 FFP transfusions in 190 hospitals, mainly given to adults (93.3%). Among these adult patients, 43% of all FFP transfusions have been administered as a prophylaxis for abnormal coagulation tests without any sign of bleeding. In addition to a wide variation of INR before FFP transfusion, 30.9% of patients received FFPs without any sign of bleeding and an INR ≤ 1.5. In a follow-up study [45], the authors found that preprocedural FFP transfusions were carried out in 15% of cases, while transfusion was even done in 36% of cases without a planned invasive procedure. The median transfused FFP dose was 10.4 ml/kg (25^{th}/75^{th} percentile, 7.2–14.4 ml/kg). FFP was transfused in 31% of

cases although the INR was within the normal range, while 41% of the cases received FFP for mild coagulopathy (INR ≤ 2.5) in the absence of bleeding. Moreover, post-transfusion improvement of INR was small unless INR was >2.5.

In 2011, Müller et al. conducted a RCT [46] to assess whether prophylactic FFP transfusion (12 ml/kg) in critically ill patients with prolonged INR undergoing invasive procedures is effective in preventing bleeding. The trial was stopped because of slow recruitment. The preliminary data published in 2015 [47] included 81 patients, 40 patients receiving FFP versus 41 patients not receiving FFP before an invasive procedure. The incidence of bleeding did not differ between the groups. One major and 13 minor bleedings occurred, with no significant difference between the two study arms (p=0.08). FFP transfusion improved INR in only 54% of the transfused patients. A meta-analysis including 21 RCTs [48] concluded that there is no evidence for either prophylactic or therapeutic FFP transfusions.

Warner et al. conducted a retrospective cohort study [49] which also confirmed that prophylactic FFP transfusion did not improve patient's outcome. Among the 27,561 patients included in the study, 2,472 patients received plasma, of whom 1,105 received plasma as a prophylaxis. In a multivariate propensity-matched analysis, the transfusion of RBC was more likely (OR = 4.3, p <0.001) and was associated with a longer hospital stay in patients receiving prophylactic FFP transfusion. There was no survival difference between the groups.

Two RCTs evaluated the role of prehospital plasma transfusion in trauma patients [50,51], one with air medical transport system and a longer transportation time (PAMPer trial) and another with ground medical transportation system and shorter transportation time (COMBAT trial). Although the 30-day mortality in the plasma group decreased from 33.0% to 23.2% (P=0.03) in the PAMPer trial, the 28-day mortality increased in the plasma group from 10% to 15% (P=0.37) in the COMBAT trial. Therefore, it is not yet clear whether plasma transfusion is beneficial or harmful in this setting [52,53].

The European RETIC RCT evaluated the reversal of trauma-induced coagulopathy by comparing first-line coagulation factor concentrates guided by ROTEM to FFP transfusion [54]. Patients received either 15 ml/kg FFP or coagulation factor concentrates guided by ROTEM. A total of 94 patients (44 in the FFP group and 50 in the coagulation factor group) were included in the planned interim analysis. A rescue treatment with coagulation factors was required in 52% of the patients in the FFP group versus only 4% of the patients in the coagulation factor concentrate group needed FFP. Therefore, the study was stopped for futility and safety reasons. Furthermore, the incidence of massive transfusion was significantly lower in the coagulation factor concentrate group (12% vs. 30%; P=0.042), while the incidence of multiple organ failure (50% vs. 66%; P=0.15) and venous thrombosis (8% vs. 18%; P=0.22) was higher in the FFP group. Finally, a meta-analysis of 15 RCTs with 755 patients undergoing cardiac surgery showed that FFP transfusion was inferior to a control for reducing RBC transfusion [55]. Return to operation theater did not differ between the groups. In summary, there is no sound of evidence for prophylactic and very low evidence for therapeutic plasma transfusion.

Platelet Transfusion

Raval, et al. demonstrated that passive reporting greatly underestimates the incidence of TACO after platelet transfusion [56]. On the one hand, a retrospective data analysis showed a platelet transfusion-related TACO rate of only 1 per 5997 platelet units transfused, while on the other hand, this rate was 1 in 167 during a 30-day period of prospective active reporting. Traditionally, the largest experience with platelet transfusion exists in hematology patients with hypoproliferative thrombocytopenia. The safe threshold for prophylactic platelet transfusion in a clinically stable patient without bleeding is a platelet count of 5–10/nl [7-9]. However, despite some evidence showed that a platelet count >10/nl is associated with a lower bleeding risk during invasive procedures, many surgeons and even intensivists insist on a platelet count of at least 50/nl to insert a central venous catheter. However, a recently published RCT demonstrated that the use of a restrictive transfusion strategy prior to central venous catheterization in patients with cirrhosis is associated with a reduction in transfusion and costs without any negative effect on bleeding [57]. Ultrasound-guided central venous catheter insertion seems to be safer compared to prophylactic platelet transfusion before catheter insertion [58].

Platelet function may be more important for the prediction of bleeding than just platelet count. However, most available platelet function analyzers are affected by a platelet count below 100-150/nl. This is also true for whole blood impedance aggregometry devices such as the Multiplate (Roche, Basel, Switzerland) and ROTEM platelet (Tem Innovations, Munich, Germany) device. The test results are dependent on platelet function as well as platelet count and can predict bleeding and thrombosis in several settings. VET may be more reliable than whole blood impedance aggregometry in patients with very severe thrombocytopenia (<30/nl). The combination of EXTEM and FIBTEM clot firmness allows for the calculation of the platelet contribution of clot firmness (PLTEM) [5,59-61]. Here, ROTEM has been shown to better correlate with bleeding in patients with severe thrombocytopenia compared to platelet count [62,63].

A Cochrane systematic review [64] that evaluated prophylactic platelet transfusion prior to surgery for patients with low platelet counts identified three RCTs with a total of only 180 patients. Among these trials, two were conducted in patients with liver disease and one trial was conducted in an intensive care setting. One trial compared platelet transfusion with a placebo, while the other two trials compared platelet transfusion with drugs that increase platelet count. The authors found insufficient evidence to recommend preprocedural platelet transfusion to avoid postoperative or postprocedural bleeding.

Zakko, et al. [65] conducted a retrospective study including 408 patients, of whom 204 were on platelet inhibitors and 204 were not. The platelet counts in all patients were above 100/nl. The patients were matched regarding bleeding episodes and age. Platelet transfusion in patients with gastrointestinal bleeding treated with antiplatelet drugs but without thrombocytopenia did not reduce rebleeding episodes but was associated with increased mortality (OR, 5.57; 95% confidence interval, 1.52-27.1). In another retrospective study, the use of platelet transfusion in 126 living donor liver transplant patients was associated with a decreased 90-day survival (78.9% vs. 94.2%, p= 0.009) [14]. This is in line with the data published by Pereboom, et al. [13] showing that patient and graft survival were significantly lower in patients receiving platelet transfusions than in those who did not (74% vs. 92% and 69% vs. 85% one-year survival, respectively) [13]. A recent study 66 evaluated the effect of prophylactic platelet transfusion in a large cohort of critically ill patients. Among 40,693 patients, 3,227 patients received platelet transfusions, of whom 1,067 received prophylactic platelet transfusions. Those patients with prophylactic platelet transfusion had a significantly higher rate of RBC transfusion (OR = 7.5, $p < 0.005$), and the sequential organ failure assessment (SOFA) score showed less significant improvement within 24 h after platelet transfusion. In a retrospective study in patients after cardiopulmonary bypass [66,67], which included 169 patients receiving platelet transfusion and 507 matched controls, no difference between the two groups regarding mortality, thromboembolic events, reintervention, infection, and organ failure could be observed. The platelet transfusion group showed less blood loss but a higher rate of vasopressor requirement, longer mechanical ventilation time, and longer Intensive Care Unit (ICU) length of stay. Currently, another RCT is running evaluating whether platelet transfusion prior to central venous catheter insertion is beneficial or not [68]. One multicenter RCT assessed the beneficial effect of platelet transfusion in patients on antiplatelet treatment suffering from spontaneous intracerebral hemorrhage (ICH) [69]. The study showed that the odds of death or dependence at three months were higher in the platelet transfusion group than in the standard group. Serious adverse events (SAEs) occurred twice as often (OR, 2.05) in the platelet transfusion group than in the placebo group.

Prophylactic or liberal platelet transfusion seems to be harmful, particularly in patients with preoperative and preprocedural thrombocytopenia, in patients with cirrhosis, gastrointestinal bleeding, or those undergoing liver transplantation, in critically ill and burn patients, in patients with traumatic brain injury or intracerebral hemorrhage, in patients with Dengue fever, as well as in neonates. In 2013, a noninferiority RCT was published for the no-prophylaxis platelet transfusion strategy in hematologic cancer patients [64]. The transfusion threshold for platelets was 10 x 10^9/L in the morning platelet count. Patients not receiving prophylaxis had more bleeding events compared with prophylactic platelet transfusions. The conclusion was that the no-prophylaxis policy was inferior compared with prophylactic platelet transfusion. On the other hand, a Cochrane analysis published in 2015 [70-102], looking at thrombocytopenic patients due to myelosuppressive chemotherapy or stem cell transplantation, found low-quality evidence that a standard trigger level (10 x 10^9/L) was associated with an increased risk of bleeding when compared with a higher trigger level (20 x 10^9/L or 30 x 10^9/L). Again, these results support the idea that assessment of platelet function is more important than platelet count. In this context, the use of VET and platelet function testing could be helpful to better identify patients who might benefit from platelet transfusion (Tables 1 & 2).

Conclusion

Patient blood management should not focus on restrictive RBC transfusion, only, but must consider inappropriate plasma and platelet transfusion as an important trigger of transfusion associated adverse events and worse patient outcomes, too. Here, the lack of evidence for prophylactic or preemptive plasma and platelet transfusion is in conflict with daily clinical practice in most hospitals around the world and risk awareness and PBM education is urgently needed. In patients with coagulopathic bleeding, current evidence favors the concept of VET-guided bleeding and patient blood management integrating the use of coagulation factor concentrates and hemostatic drugs if available.

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Authors Contribution

FS made substantial contributions to the conception or design of the work and wrote the manuscript.

DD critically revised the manuscript for important intellectual content.

SP made a substantial contribution to the analysis and interpretation of the data and critically revised the manuscript for important intellectual content.

KG conducted the literature search, drafted the manuscript, and contributed important intellectual content.

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KG works as the Medical Director of Tem Innovations/ Instrumentation Laboratory PBM since July 2012.

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