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Infusible Platelet Membrane versus Conventional Platelet Concentrate: Benefits and Disadvantages

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Abstract

Blood transfusion centers are under considerable pressure to produce platelet concentrates with a shelf life limit of 3 to 5 days. Many approaches have been investigated experimentally to produce new hemostatically active platelet products that are capable of long term storage. In this article infusible platelet membrane will be explained as a platelet substitute versus conventional liquid-stored platelet concentrates with regard to their benefits and disadvantages in transfusion medicine. This review shows that lyophilized infusible platelet membrane as a platelet substitute might offer many important benefits over common platelet concentrates with few disadvantages. Infusible platelet membrane may have efficacy, safety and acceptable tolerability without thrombogenecity, immunogenicity or toxicity. The other main benefits of this product are improved shelf life, ease of storage, high-precision dose calculation, easy reformulation, reduced viral and bacterial load, decreased refractoriness to platelet transfusion, reduced contaminating red and white blood cells, reduced side effects due to removal of undesirable effects of intracellular and extracellular proinflamatory mediators and removal of platelet-derived microparticlecs as a source of CD40/CD40L ligands, which can enhance post-transfusion reactions, achieving hemostatic response without increasing the circulating platelet count, not being removed from circulation by immune mechanisms or sepsis and not requiring blood typing. In spite of these benefits, there are still some difficulties in demonstrating its efficacy, short-term circulation and hemostatic function. Therefore, further human clinical studies will be needed to fully define the exact role of infusible platelet membrane in the management of patients with thrombocytopenia.

Keywords: Infusible platelet membrane, platelet, substitute, platelet concentrates, side effects.

Introduction

Platelet concentrates are usually stored in blood transfusion centers for 3 to 5 days, then they are discarded; therefore, blood transfusion centers are under considerable pressure to produce platelet concentrates for transfusion. Many approaches have been explored experimentally to produce novel hemostatically active platelet products that are capable of long-term storage [1-4]. These include: frozen platelet storage, liquid cold (4ºC) storage, rehydrated lyophilized platelets, and platelet membrane microparticles. Platelets play a dual role in hemostasis. First, they show adhesion and aggregation properties at sites of vascular lesion [5,6]. Second, the exposure of anionic phospholipids on the surface of activated platelets acts as a catalytic site for the initiation of coagulation cascade that will strengthen initial hemostatic plug formation [7,8]. This review summarizes previous in vitro, pre-clinical and clinical studies of infusible platelet membrane (IPM) versus conventional platelet concentrates in order to compare their benefits and disadvantages.

Conventional liquid-stored platelet concentrates

Platelet concentrates for transfusion into bleeding thrombocytopenic patients have been available for routine clinical use for 5 decades. Transfusion adverse reactions such as fever, rigors, and more rarely, life-threatening acute injury, occur to 30% of platelet transfusion recipients, which is

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significantly higher than red cell transfusions [9]. Currently platelet concentrates can be transfused up to five days after preparation, but there is a concern that platelet efficacy and safety may decline during storage due to platelet activation which increases over time. Other issues that might be involved in this "storage lesion" are platelet surface P-selectin [10] and platelet-derived soluble mediators, histamine [11], CD40 ligand (CD40L) [12], regulated on activation normal T cell expressed and secreted protein (RANTES), platelet factor 4 (CXCR4), transforming growth factor-β and CXCL8 (IL-8) [10]. Besides enhancing platelet activation, increased soluble CD40L levels have been associated with an increased risk of allergic and febrile reactions in platelet transfusion recipients, as well as lung injury [13,14]. A recent report has indicated that platelet-derived microparticles which carried the sCD40L, accumulated in the platelet concentrates during the 5 days of storage, which might induce transfusion adverse events such as transfusion related acute lung injury (TRALI) [15]. Once platelets become activated to release these mediators, they may well be less effective in hemostasis upon transfusion. In addition to changes in soluble mediators, the entire platelet proteome has also been shown to change over time in storage, which can lead to their functional decline [16,17]. Refractoriness, the inability to increase platelet counts post-transfusion due to ABO-incompatibility [18-20], exposed Human Leukocyte Antigen (HLA)-A, and the presence of B proteins on the platelet surface are other common complications [21,22]. In addition, transfused platelets can contribute to inflammation and organ injury by the release of α-granule mediators and cytokines [23-26]. Moreover, platelet transfusions may be associated with thrombosis, contributing to common conditions such as acute coronary syndrome, ischemic stroke, transient ischemic attack and deep vein thrombosis [27-30]. It may be concluded that during storage for transfusion, platelets experience decreased efficacy/viability, while levels of prothrombotic and proinflammatory soluble mediators and microparticles increase. This trend could be due to activation and platelet death within the unit. On the other hand, the method of platelet preparation can play a significant role in platelet activation due to effects of centrifugation speed on platelet aggregation activity [31,32].

Bacterial contamination occurs in about 1/3000 platelet units and can lead to sepsis in 1 out of 6 contaminated products [33], which appears to represent a greater risk than that associated with other blood products. This is in large part because platelet concentrates must be kept at a temperature of 22° ± 2°C during storage; therefore, unlike red blood cells bacterial growth is not inhibited by low temperature storage.

Infusible platelet membrane

Previous in vitro experiments have confirmed that lysed platelets shorten prolonged coagulation times [34,35]. Preliminary studies in animals showed that disintegrated platelets are toxic and may not be effective [36,37]. When large amounts of these platelets were given intravenously over a short period of time, severe circulatory and respiratory effects were regularly observed in irradiated thrombocytopenic dogs [38] and this also had a marked effect on prothrombin consumption. It was interpreted that these side effects are caused mainly by serotonin when they were markedly reduced when dogs were given a serotonin analogue for 4 days before transfusions [39]. On the other hand, some clinical observations in thrombocytopenic patients showed that platelets may have hemostatic effect, even if they are not intact and improve hemostasis with no evidence of serious toxicity or thrombosis [37,40]. Due to side effects problems, this sort of investigations was abandoned for nearly three decades because these materials produced considerable distress in experimental animals [38] until experiments in thrombocytopenic rabbits with infusible platelet membrane indicated preclinical evidence of their hemostatic efficacy without significant morbidity [41]. Methods for storage of platelets in liquid state or by cryopreservation yield many lysed platelets and membrane vesicles [42,43]. Transfusion of theses infusible platelet membrane vesicles into rabbits at various levels of thrombocytopenia has shown that hemostasis can be achieved without an increase in circulating platelet count and that platelet membrane vesicles induce reductions in bleeding times [41,44-46]. In contrast, some other studies have concluded that blood bank platelets must be intact and circulate for a hemostatic response to be achieved and that the indication of a successful platelet transfusion is an increase in circulating platelet count [47-50]. One company, Cypress Bioscience Incorporated (San Diego, CA, USA)

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has manufactured a microparticulate, known as IPM Cyplex™ from outdated blood bank human platelets by lysis and differential centrifugation and treatment to inactivate blood-borne viruses [44]. IPM has been successfully administrated in normal human volunteers and thrombocytopenic patients in phase I and II clinical trials. The phase II trials have been performed among bleeding refractory thrombocytopenic patients and have provided some indication of improvement (cessation of bleeding) in some patients [3]. Results of phase III clinical trials are awaited. It should be noted that, this product has not yet been licensed by the FDA because of the difficulties in demonstrating efficacy. The efficacy of this product in platelet transfusion cases that have developed antibodies to HLA and platelet antigens is under investigation. It is difficult to determine the effects of any platelet substitutes in thrombocytopenic patients since they typically have other conditions associated with a bleeding tendency. Furthermore, evaluation of efficacy of a platelet substitute is difficult because major bleeding due to platelet dysfunction is rare [51]. Perfusion methods such as the one explained by Baumgartner [52] have facilitated the investigation of mechanisms involved in hemostatic function of platelet concentrates. Different researchers have used these perfusion techniques to evaluate the impact of different storage conditions on platelet reactivity [53-57]. The results of perfusion studies have shown that platelet fragments or nonviable platelets (IPM) [58-61] and synthetic phospholipids [62] promote a procoagulant activity that can be proved on the surface of damaged cells. A preliminary clinical study of lyophilized platelet material in patients with secondary thrombocytopenia has indicated no toxicity or thromboembolic sequelae 40. A study on thrombogenecity of IPM by Wessler et al. 63 has indicated that IPM is not thrombogenic 44. In normal human volunteers, infusions of IPM were well tolerated and had no effect on biochemical or coagulation parameters and no evidence of immunogenicity was reported [3]. As general, little has been published on the effects of manufacturing processes on intrinsic platelet antigens and neoantigen formation for platelet products and substitutes. The risk of infection with IPM product is very low due to the applied pasteurization treatment in IPM [64] as well as plasma products [65-66].

Infusion of large amounts of disintegrated platelets over a short period of time has caused severe circulatory and respiratory effects in irradiated dogs due to the presence of serotonin [39]. Similarly, infusion of stored and frozen platelets (-15˚C up to 6 weeks) without cryoprotectant to severely thrombocytopenic patients has led to transient elevation of the blood pressure and local constriction due to the presence of serotonin, with no evidence of serious toxicity or thrombosis [37].

With respect to hemostatic effectiveness, significant reduction of bleeding time has been reported by infusion of stored platelet membrane vesicles (for up to 6 months at -65˚C) to thrombocytopenic rabbits [39]. Different studies have shown that IPM (2 mg/kg) can shorten the prolonged bleeding time in thrombocytopenic rabbits for at least 6 h after infusion [44,45]; by 24 h this hemostatic effect was no longer detectable. Administration of IPM at 4 mg/kg has been shown to change bleeding time from 900 to 450 seconds in thrombocytopenic rabbits [51]. In another study, patients with platelet counts less than 50 x 10^9 /L and mucosal hemorrhage received either a single dose of IPM (ranging from 2 to 6 mg/kg) or standard platelet concentrate. Improvement or complete cessation of bleeding was reported in 17 of 26 (65%) treated with IPM and 3 of 5 (60%) who received conventional platelet concentrates [41]. In one investigation, normal human volunteers received IPM at a maximum dose of 6 mg/kg over 30 to 40 minutes. They received aspirin orally before the infusion of IPM and the volunteers with the prolonged bleeding time were selected. The administration of IPM in these volunteers shortened the bleeding time and none of patients appeared to develop antibodies to IPM as determined by flow cytometry [3]. In another study, 6 of 8 thrombocytopenic patients receiving 3 or 6 mg/kg of IPM had a shortening of at least one of 2 or 3 bleeding times performed after infusion; however, shorter bleeding times were also observed in 2 of 2 patients after infusion of placebo [67]. In another report, a randomized, dose-ranging study was performed to determine the safety and efficacy of IPM on patients aged 18 to 70 years who had moderate active bleeding with platelet count less than 50 × 10^9/L. Ten patients received IPM (6 mg/kg) and 2 received random-donor platelets. In 7 of 10 (70%) patients treated with IPM and in both

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patients who received random-donor platelets, bleeding decreased or stopped. When evaluating the refractoriness to platelet transfusion, 2 of 4 (50%) patients who were refractory to platelets responded to IPM, while 5 of 6 (83%) patients who were not refractory to platelets did so. Furthermore, one refractory patient who did not respond to IPM had an obvious increment in platelet count after receiving a platelet transfusion and it was concluded that IPM may decrease refractoriness to platelet transfusion [3].

Discussion

It seems that IPM as a platelet substitute might demonstrate efficacy, safety, acceptable tolerability without thrombogenecity, immunogenicity or toxicity. In spite of challenges in demonstrating its efficacy, investigations should continue to provide maximal clinical benefits with minimal risk of complications [68,69].

The proposed advantages of IPM over products containing intact platelets include:

- Improved shelf life, ease of storage and use.
- Reduced viral and bacterial load.
- Reduced expression of human leukocyte antigen (HLA) class 1 antigens.
- Being prepared from outdated platelets so can be more easily accessible for mass procurement.
- May decrease refractoriness to platelet transfusion.
- Reduced contaminating red and white blood cells which can promote antibody formation against them.
- Reduced side effects due to removal of undesirable effects of intracellular and extracellular proinflamatory mediators such as serotonin, cytokines and chemokines.
- Reduced side effects due to removal of platelet-derived microparticlecs, as a source of CD40/ CD40L ligands, which can enhance post-transfusion reactions.
- Achieving hemostatic response without increasing circulating platelet count which is the main part of a successful platelet transfusion.
- Not being removed from circulation by immune mechanisms or sepsis.
- Not being entrapped in the spleen and microvasculature by virtue of their smaller size.
- Having a high-precision dose calculation and easy reformulation.
- Not requiring blood typing, so it can be infused immediately and for patient with all blood types.
- May reduce side effect of transfusion-associated circulatory overload (TACO) due to lower volume administration.

The disadvantages of IPM over platelet concentrates include:

- Short-term circulation and hemostatic function.
- Not being more effective in comparison with fresh intact platelet units in ordinary doses.
- More difficult to quantify its effects in thrombocytopenic patients who typically have other conditions associated with a bleeding tendency.
- Not suitable for rapid administration.

Conclusion

It may be deduced that the main challenge for IPM as a platelet substitute is its efficiency in human clinical trial studies. However, it may be realized that not all platelet properties have to be covered by a platelet substitute. Such a substitute may be able to replace certain aspects of platelet function and may be appropriate in specific clinical situations. However, further human clinical studies are required to more fully define the exact role of platelet membranes as a drug in the management of patients with thrombocytopenia.

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