Thrombosis & Haemostasis: Research

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Editorial

Infusible Platelet Membrane may be Effective and Safe: A Mini Review

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Received: January 21, 2019; **Accepted:** March 21, 2019; **Published:** March 28, 2019

Editorial

Platelets are small, disc shaped cells that have a critical role in helping our blood clot and stop bleeding. 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 investigated experimentally to produce novel hemostatically active platelet products that are capable of long-term storage [1].

Infusible Platelet Membrane (IPM) as a platelet substitute may be the most feasible approach to reach the target market [2]. Previous *in vitro* experiments have confirmed that lysed platelets shorten prolonged coagulation times [3,4]. Preliminary studies in animals showed that disintegrated platelets are toxic and may not be effective [5,6]. 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 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 [7,8]. Due to side effects problems, this sort of investigations was abandoned for nearly three decades because these materials produced considerable distress in experimental animals [7], until experiments in thrombocytopenic rabbits with infusible platelet membrane indicated preclinical evidence of their hemostatic efficacy without significant morbidity [9]. 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 [6,10].

One company, Cypress Bioscience Incorporated (San Diego, CA, USA) has manufactured a microparticulate, known as IPM Cyplex™ from fresh or outdated blood bank human platelets by lysis and differential centrifugation and treatment to inactivate blood-borne viruses [11]. IPM has been successfully administrated in normal human volunteers and thrombocytopenic patients in phase I and II clinical trials and have provided some indication of improvement (cessation of bleeding) in some patients with a single dose of IPM (ranging from 2 to 6 mg/kg) [12-14]. Results of phase III clinical trials were not reported. This might be due to the difficulties in demonstrating IPM efficacy.

The results of perfusion studies have shown that platelet fragments or nonviable platelets (IPM) [15,16] and synthetic phospholipids [17] promote a procoagulant activity that can be demonstrated on the surface of damaged cells.

Our recent experiences have shown that major platelet adhesion (CD41b) and aggregation (CD41/CD61) receptors presence on the membrane with platelet factor 3 activity in lyophilized IPM preparation [18]. As well, our newer animal studies of IPM have demonstrated its efficacy with dose-dependent property [19,20], without any pyrogenic side effect [21] or toxicity [22]. Nasiri et al results in rabbits showed that the maximum hemostatic effectiveness was at 2 hours after IPM administration, while Chao et al had been reported 4 hours [11]. Also, the major aggregation receptor of platelets CD41/CD61 was present on our IPM, but was absent in Chao experiment may be due to our modified IPM processing with lower detrimental effects on platelet membrane receptors. These findings confirms more improving of its hemostatic effectiveness.

In brief, although platelet concentrate transfusions are highly effective in many clinical conditions but the rate of transfusion reactions is rather high. In addition to febrile non-hemolytic transfusion reactions, transfusion-associated graft-*versus*-host disease, allergic and anaphylactic reactions, rare but dangerous transfusion reactions related to platelet concentrates such as transfusion-related acute lung injury, septic complications induced by bacterially contaminated products, and hemolytic transfusion reaction may be observed [23]. On the opposite side, previous and recent studies have shown that IPM may promote lower side effects with acceptable tolerability, without any adverse effects on biochemical or coagulation indices, no evidence of thrombogenicity, immunogenicity or toxicity, by removal of extracellular and intracellular immune and non-immune proinflamatory mediators. Thus, IPM may be safer than conventional platelet concentrates, but its effectiveness, as a platelet substitute needs to be more confirmed. It seems that further human clinical studies are required in the all aspects to more fully define the exact role of platelet membranes as a drug in the management of patients with thrombocytopenia.

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Citation: Nasiri S. Infusible Platelet Membrane may be Effective and Safe: A Mini Review. Thromb Haemost Res. 2019; 3(1): 1021.

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Thromb Haemost Res - Volume 3 Issue 1 - 2019

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