Title

Red blood cell aggregation; an important phenomenon in damage control resuscitation?

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Abstract

To improve the survival of severely bleeding trauma patients, a damage control resuscitation concept has been recommended. This concept includes the early infusion of red blood cells (RBCs), fresh frozen plasma (FFP) and platelets into a 1:1:1 unit ratio to control the bleeding. Although lower FFP ratios have been linked to higher rates of mortality, higher ratios have been associated with adverse outcomes as well. The formation of RBC aggregates in regions with low flow could play a key role in these findings. Although fibrinogen content and thus FFP is essential for coagulation, it also induces the formation of RBC aggregates. Physiological levels of aggregation are necessary to maintain flow dynamics. However, under certain pathologic conditions stronger and larger aggregates are formed, which may hinder or obstruct the blood flow in micro-vessels. Notably, enhanced aggregation has also been observed due to hyperfibrinogemia. We consider that RBC aggregation can play an important role in damage control resuscitation and that excessive administration of FFP could augment the RBC aggregation process and contribute to the deleterious effects of this practice.
Uncontrolled bleeding is the leading cause of death in trauma patients. It was recognized that approximately 25% of severely injured trauma patients are coagulopathic upon admission and that these patients are three times more likely to die than those without it [1]. This acute coagulopathy of trauma has been attributed to a combination of multiple factors such as loss, dilution and consumption of coagulation factors and platelets as well as to fibrinolysis, hypothermia and metabolic acidosis [2]. To improve survival of severely injured trauma patients, an early damage control resuscitation concept has been recommended. This resuscitation approach primarily advocates limited crystalloid use, prevention and treatment of acidosis and hypothermia, as well as the early administration of red blood cells (RBCs), fresh frozen plasma (FFP) and platelets in a 1:1:1 unit ratio [3]. Although the optimal blood component ratio is still a matter of debate, the general consensus is that an early resuscitation approach controls the bleeding and potential favors survival of trauma patients [4].

Limited attention has been addressed to the mechanistic link attributing to the improved survival. Recently, the improved survival has been linked to inhibition of vascular endothelial permeability and subsequently diminished interstitial edema [5]. Yet the ability of RBCs to form aggregates in the presence of plasma proteins, such as fibrinogen, α2-macroglobulin and albumin, may also play a pivotal role in damage control resuscitation. The reversible formation of RBC aggregates in low flow areas is a physiological phenomenon that has been studied for decades. Although RBC aggregation has shown to be an important determinant of the blood viscosity, the physiological role of the aggregation process still remains unclear. The increasing blood flow is normally sufficient to disperse RBC aggregates. However, under pathological conditions stronger and or larger aggregates may form which are more resistant to dispersion by shear forces.
Enhanced RBC aggregation can impair the blood flow in the microcirculation and contribute to the occlusion of micro-vessels, which may induce local hypoxia and damage to endothelial cells [6,7]. Aggregation of RBCs is difficult to assess, however the laser-assisted optical rotational red cell analyzer (LORCA; R&R Mechatronics, the Netherlands) is a useful technique, which allows RBC aggregation behavior to be studied ex vivo. With this technique, enhanced RBC aggregation has been demonstrated in a variety of pathological states including critical illness [8].

Coagulation is a complex process, in which a damaged endothelium initiates a cascade of pathways leading to the formation of a clot at the site of injury. In cases of massive bleeding, fibrinogen is the first coagulation factor that reaches critically low levels. Administration of blood products in an 1:1:1 unit ratio will replenish depleted coagulation factors and platelets and minimize dilutional coagulopathy, as is the case when only RBCs or volume expanders will be administrated [9]. In a trauma setting the use of FFP in massive bleedings has also been questioned. Adverse outcome such as increased incidence of nosocomial infections, multiple organ failure, lung injury and even death have been linked to the usage of FFP [10]. Studies have shown mixed results, but in general, higher ratios of FFP have been associated with adverse outcomes whereas lower ratios of FFP have been linked to increased rates of mortality [1].

For many years, it has been recognized that RBCs can actively participate in clot formation by promoting platelet degranulation, mediating platelet aggregation and by recruitment of additional platelets into the forming clot [11]. The role of RBC aggregation in haemostasis has been given less attention. RBCs migrate from the endothelial wall into the center of the blood vessel where they form aggregates. RBC aggregates exclude leukocytes and possibly platelets from the axial core and direct them towards the vascular wall [12]. This process is essential since leukocytes and platelets
need to get into close contact with the damaged endothelium, in order to exert their function. Recently it was proposed that the lower aggregation tendency of leukoreduced prolonged stored RBCs could indeed contribute to a reduced haemostasis [13].

Infusion of RBCs, FFP and platelets in a 1:1:1 unit ratio will provide slightly less components than in the case when whole blood is used [3]. If aggregation plays a role in damage control resuscitation, one can speculate that infusion of blood components with a composition that approximates whole blood would be beneficial for supporting haemostasis in severely injured trauma patients. Conversely, adoption of a more liberal policy with regard to FFP could potentially tip the balance and augment RBC aggregation in these patients, which could subsequently hamper tissue perfusion and contribute to the occlusion of micro-vessels. Particularly, since enhanced RBC aggregation due to hyper-fibrinogenemia has been considered a significant risk factor of microcirculatory disorders in a subset of patients [7]. Likewise, in patients with increased risk of deep venous thrombosis, enhanced RBC aggregation and elevated fibrinogen levels were evident [14]. It is therefore likely that enhanced aggregation of RBCs could contribute to the adverse effects recorded with the use of FFP. Enhanced RBC aggregation, which was also evident during long-term storage of non leukoreduced RBCs, could furthermore explain the finding that fresh whole blood was more effective than blood component infusion, in improving the survival of trauma patients [3,15]. The above data underline the potential importance of physiological levels of RBC aggregation in maintaining haemodynamics.

Most studies regarding resuscitation practices are retrospective. Although these studies are limited inherently to their retrospective design, they do provide interesting hypotheses. Early FFP infusion is considered lifesaving in severely bleeding trauma patients. Yet, to determine appropriate blood component ratio’s, ex vivo RBC aggregation testing will be helpful in elucidating the role of RBC aggregation in damage
control resuscitation. In addition, prospective randomized controlled trials in severely injured trauma patients are ultimately necessary.

**Abbreviations**

RBCs = red blood cells, FFP = fresh frozen plasma.

**Conflict of interest**

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