Rheologic changes of hypothermic preserved red blood cells

Henkelman, Sandra

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2012

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Chapter 3

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

Sandra Henkelman
Michael Piagnerelli
Gerhard Rakhorst
Abstract

To improve the survival of severely bleeding trauma patients, a damage control resuscitation strategy has been recommended. This strategy includes the early infusion of fresh frozen plasma (FFP), platelets and RBCs in a 1:1:1 unit ratio to control the bleeding and favor survival of these patients. Although lower FFP to RBC ratios have been linked to higher rates of mortality, these high ratios have been associated with adverse outcomes as well. The formation of RBC aggregates in regions with low shear rate could play a key role in these findings. Administration of FFP and thus fibrinogen is essential for coagulation. Yet, fibrinogen also promotes RBC aggregation. Although physiological levels of RBC aggregation support the hemostasis, promotion of aggregation could be disadvantageous in patients in which the RBC rheology is already compromised, as was observed in certain trauma states. Notably, enhanced RBC aggregation may hinder tissue perfusion and contribute to the occlusion of micro-vessels. We consider that RBC aggregation could play an important role in damage control resuscitation of severely injured trauma patients.
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 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 the survival of severely bleeding trauma patients, an early damage control resuscitation strategy has been recommended. This resuscitation approach primarily advocates limited crystalloid use, prevention and treatment of acidosis and hypothermia, as well as an early administration of fresh frozen plasma (FFP), platelets and RBCs 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 with this high FFP to RBC ratio, controls the bleeding and potentially favors survival of severely bleeding trauma patients.\(^4\)

Limited attention has been addressed, to the mechanism by which a high FFP to RBC ratio influences survival in these trauma patients. 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, especially fibrinogen, could also play a pivotal role in damage control resuscitation.

The formation of RBC aggregates in regions with low shear rate is a physiological phenomenon that has been studied for decades. Although RBC aggregation is a major determinant of the whole blood viscosity at low shear rate, the physiological role of this process is still elusive. Under normal physiological conditions, RBC aggregates are easily dispersed by the rise in blood flow rate. However, under pathological conditions stronger and or larger RBC aggregates are formed which are more resistant to dispersion by shear forces. Enhanced RBC aggregation may 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.\(^6,7\) In this regard, the LORCA is a useful device, which allows RBC aggregation to be studied ex vivo.

In cases of massive bleeding, fibrinogen is the first coagulation factor that reaches critically low levels. Administration of blood components 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.\(^8\) Yet, 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 death have been linked to the usage of FFP.\textsuperscript{9} Studies have shown mixed results, but in general, high FFP to RBC ratios have been associated with adverse outcomes whereas low FFP to RBC ratios have been linked to increased rates of mortality.\textsuperscript{1,10}

For many years, it has been recognized that RBCs can actively participate in clot formation by enhancing platelet de-granulation and by recruitment of additional platelets into the forming clot.\textsuperscript{11} The role of RBC aggregation in hemostasis 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.\textsuperscript{12,13} This process is essential since leukocytes and platelets need to get into close contact with the damaged endothelium, in order to exert their function.

RBC aggregation increases proportionally with fibrinogen levels.\textsuperscript{14} Administration of FFP, platelets and RBCs in a 1:1:1 unit ratio, a composition that approximates whole blood, could promote RBC aggregation. On the one hand promotion of aggregation would be beneficial for supporting hemostasis in severely injured trauma patients. Especially, since it has been recognized that people with leukocyte adherence deficiency suffer from recurrent bacterial infections and impaired wound healing and because it has been recognized that infections remain a concerning complication of combat-related injuries.\textsuperscript{15,16} On the other hand, promotion of aggregation could be detrimental to patients in which the RBC rheology is already compromised, as was observed in certain trauma states.\textsuperscript{17-19} In this regard, enhanced RBC aggregation could subsequently hamper tissue perfusion and contribute to the occlusion of micro-vessels. Enhanced RBC aggregation, which was also evident during long-term storage of non-leukoreduced RBC units, could furthermore explain the finding that blood component infusion was less effective than fresh whole blood in supporting hemostasis of trauma patients.\textsuperscript{3,20,21} The above mentioned data underline the potential importance of RBC aggregation in damage control resuscitation.

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 the influence of high FFP to RBC ratios on promoting RBC aggregation in these patients, ex vivo aggregation testing will be necessary. In this regard, the LORCA could be
useful to demonstrate RBC aggregation tendencies after damage control resuscitation of severely bleeding trauma patients.

References


