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Bleeding, Coagulopathy and Blood Products in Major Trauma

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Transfusion of blood components in trauma can be lifesaving. Evidence for existing practice is being challenged, potentially with major blood supply implications, and novel therapies are under investigation.

Introduction

The first human blood transfusion was performed in 1818 (Giangrande 2000), but not until the antigens distinguishing major blood groups were described in 1901 did transfusion become acceptably safe, at least for patients in the greatest need. Transfusion-transmitted infection is now a negligible hazard; other obvious adverse events (see Table 1 (Australian Red Cross Blood Service 2014)) are more common but largely amenable to treatment. Concern over subtler effects on immunity and inflammation is more recent, and emerged in the era of evidence-based medicine, leading to several large effectiveness trials, many of which are soon to report. A worldwide strategy known as “Patient Blood Management”(PBM)(2011) aims “to improve clinical outcomes by avoiding unnecessary exposure to blood components”. Stopping bleeding is an obvious primary goal. However, seemingly in opposition to the blood-sparing goal of PBM, military and civilian trauma data show benefit from early blood (as opposed to non-blood fluid) resuscitation. Reconciling competing risks of early blood administration, blood avoidance, and more expensive blood substitutes and factor concentrates is now the subject of much research.

Stopping Bleeding

Haemorrhage is the most frequent potentially preventable cause of death, both in civilian trauma (Evans et al. 2010) and on the battlefield (Champion et al. 2003; Eastridge et al. 2012) . Prehospital extremity tourniquets improve survival (Kragh Jr. et al. 2011); junctional (Klotz et al. 2014) and abdominal aortic (Taylor et al. 2013) tourniquets and endovascular balloon occlusion of the aorta (Brenner et al. 2013) show promise for more proximal wounds. Surgical management including preperitoneal packing, advanced imaging and an abbreviated “damage control” approach (Beckett and Tien 2013) all reduce bleeding and logically should reduce mortality.

Coagulopathy of Trauma

Trauma has an initially coagulopathic (Frith et al. 2010) and later procoagulant effect (Holley and Reade 2013), which suggests that early interventions to reduce coagulopathy may be helpful, but require careful longer-term evaluation. Coagulopathic trauma patients have modest falls in clotting factors, exacerbated by crystalloid fluid resuscitation, but a profound (>350%) increase in anticoagulant activated protein C (Cohen et al. 2013) . Trauma-induced hypoperfusion and tissue damage also enhance fibrinolysis, causing an endogenous “acute traumatic coagulopathy” (ATC) (Frith et al. 2010) that may be quantitatively more important than clotting factor dilution, hypothermia or acidosis.

Massive Transfusion Protocols

The apparent reduction in major trauma mortality associated with higher ratios of plasma (Borgman et al. 2007) and platelets (Holcomb et al. 2008) to red cell resuscitation may be confounded by indication bias (Ho et al. 2012), but is nonetheless sufficiently intuitive to have been incorporated into national (National Blood Authority 2011) and international (Spahn et al. 2013) guidelines. Benefit may relate as much to preservation of endothelial integrity as to clotting factor concentrations (Jenkins et al. 2014). Up to 10% of military and 5% of civilian trauma patients require >10 units red cells transfused in 24 hours (Young et al. 2011), and protocolisation of at least the first few units results in greater efficiency (O'Keeffe et al. 2008). Point-of-care viscoelastic coagulation testing is feasible, and although demonstrating patient outcome benefit in trauma may be impossible, is associated with reduced use of blood products (Görlinger et al. 2012).

Fresh Whole Blood

Whole blood, either warm / fresh or stored at 4°C for up to 21 days (Murdock et al. 2014), is a seemingly attractive alternative to component therapy. Over 6000 whole blood units were transfused in the wars in Iraq and Afghanistan, primarily due to supply issues (Spinella 2008). Theoretical risks include allergic reactions, transfusion-associated graft vs. host disease and transfusion-transmitted infection. A pilot 107-patient trial comparing leucodepleted cold-stored whole blood with component therapy suggested a lesser transfusion requirement in patients randomised to whole blood, (Cotton et al. 2013) with no more adverse effects. A definitive study has been proposed (Murdock et al. 2014).

Alternatives to Conventional Whole Blood and Blood Components

Lyophilised plasma was introduced during the second world war, but abandoned due to the transmission of hepatitis (Inaba 2011). Having now overcome this risk, the logistic advantage of a freeze- or spray- dried product stored at room temperature has excited considerable interest, particularly from the U.S. military. Currently used by the German, French and select U.S. units in Afghanistan (Jenkins et al. 2014), the U.S. military is funding a spray-dried solvent and detergent-treated type-specific pooled product (Resusix®, Entegrion, Research Triangle Park, NC, United States) that is yet to enter a phase III trial.

Conventional room temperature stored platelets have a shelf life of only five days, making their supply difficult outside large hospitals with predictably high demand. Various platelet analogues have been developed, including infusible platelet membranes, fibrinogen/thrombin microparticles, albumin microspheres coated with human fibrinogen (Modery-Pawlowski et al. 2013), and liposomes carrying fibrinogen g-chains and adenosine diphosphate (ADP) (Nishikawa et al. 2012). None has yet reported phase III results. Platelets can also be cryopreserved in dimethylsulphoxide, extending their shelf life to two years. Although used in clinical practice by the Netherlands military since 2001, only now are two groups preparing for definitive phase III trials (Dumont et al. 2014.)

No artificial oxygen carrier has found universal acceptance. PolyHeme, a polymerised human haemoglobin, was assessed in a 714-patient trial that found no difference in mortality compared to red cell transfusion but more adverse events (Moore et al. 2009); the manufacturer subsequently became insolvent. Bovine cross-linked haemoglobin (Hemopure; HBOC-201) allowed 59.4% of 350 patients to avoid red cell transfusion, but produced more adverse events than in 338 controls (Jahr et al. 2008), and is currently registered for use only in South Africa. Polyethylene glycol-coupled haemoglobin is reported to be in early clinical trials, as are two perfluorocarbon-based emulsions. Glycerol-cryopreserved red blood cells have been used by U.S. and Dutch armed forces and recently introduced into Australian military practice, based on extensive clinical experience rather than comparative trials (Holley et al. 2013).

Pharmacological Treatment of Coagulopathy

Supra-physiologic doses of clotting factor concentrates raise the possibility that ATC may be actively treated. Factor VIIa reduced blood product use but had no effect on mortality (Boffard et al. 2005; Hauser et al. 2010) . European guidelines recommend factor VIIa be considered only if other measures have been unsuccessful. Fibrinogen is the first clotting factor to fall below critical levels in trauma. Fresh frozen plasma contains only 2g/L fibrinogen, whereas cryoprecipitate contains 8-16 g/L and fibrinogen concentrate 20g/L. Fibrinogen concentrate reduces the need for blood transfusion in cardiac surgery (Görlinger et al. 2011), but there are currently no trials and little observational evidence in trauma (Aubron et al. 2014). Lyophilised prothrombin complex concentrates (either 3-factor, with low factor VII, or 4-factor, with high factor VII) are well established for the reversal of vitamin K-dependent anticoagulants, and may have a role in trauma. Compared to plasma-based resuscitation, thromboelastograph-guided fibrinogen + prothrombin-complex concentrate reduced red cell and platelet requirements (Schöchl et al. 2011). Tranexamic acid blocks plasminogen activation, and so reduces fibrinolysis in addition to less well-characterised effects on inflammation. Tranexamic acid reduced mortality from 16% to 14.5% in the 20,211 patient CRASH2 trial (CRASH-2 trial collaborators 2010). Extrapolation of these results to prehospital care in the developed world is the subject of the PATCH-Trauma trial, currently underway (Mitra et al. 2014).

Table 1. Estimated Incidence of Tranfusion-Related Adverse Reactions (Australian Red Cross Blood Service 2014)

		Incidence (rate per total number of transfusions)
Haemolytic transfusion reaction due to ABO/Rh/other mismatch	Acute Fatal	1:76,000 1:1.8 million
Delayed haemolytic transfusion reaction		1:2,500-1:11,000
Febrile non-haemolytic transfusion reactions	Assuming universal leukocyte depletion	0.1%-1%
Allergic (IgE-mediated) reaction	Mild Severe (anaphylaxis)	1%-3% 1:20,000 – 1:50,000
Transfusion-associated acute lung injury	Male plasma confers less risk; the wide range reported reflects differing ability to supply all-male plasma.	1:1,200-1:190,000
Post-transfusion purpura		Rare
Transfusion-associated graft vs. host disease		Rare
Alloimmunisation	RBC antigens HLA anitgens	1:100 1:10
Transfusion-associated sepsis	Platelet transfusion Red cell transfusion	1:75,000 1:500,000
Transfusion-associated circulatory overload		<1%
Iron overload	Requiring chelation therapy Causing organ dysfunction if not treated	After 10-20 red cell units After 50-100 red cell units
Complications of massive transfusion	Hypothermia, coagulopathy, hypocalcaemia, kyperkalaemia	Variable (depends on quantity of product transfused, intercurrent treatments, and underlying patient condition)
Transmission of viral infection	Human immunodeficiency virus Hepatitis C Hepatitis B Human T-cell lymphoma virus Variant Creutzfeld-Jacob disease Malaria	<1:1,000,000 <1:1,000,000 1:538,000 <1:1,000,000 Theoretically possible <1:1,000,000

Effectiveness Trials Currently Underway

PROPPR (University of Texas Health Science Center, Houston) randomised approximately 680 patients expected to require a massive transfusion to plasma:platelets:PRBC 1:1:1 vs. 1:1:2. Recruitment was completed in December 2013. The Age of Blood Evaluation (ABLE) trial (Sainte-Justine Hospital Research Centre) randomised approximately 2500 patients requiring red cell transfusion to cells <8 days storage vs. standard care (2-42 days storage). The Red Cell Storage Duration study (RECESS) (New England Research Institutes) is randomising 1648 cardiac surgical patients requiring red cells to cells ≤ 10 days or ≥ 21 days, and the TRANSFUSE trial (Australian and New Zealand Intensive Care Research Centre) is randomising approximately 5000 ICU patients to standard-age red cells or the freshest available red cells in the hospital.

Management Issues – Cost-Effectiveness at a Population Level

Blood is a scarce resource. The World Health Organization recommends voluntary, non-remunerated blood donation (WHO Expert Group 2012), although there is some evidence that economic rewards do not increase risk of transfusion-transmitted infection (Lacetera et al. 2013), and are effective in increasing donor rates (Iajya et al. 2013). In Australia in 2011-2012, only 3.4% of red cell, 8.4% fresh frozen plasma, and 16.5% platelet units issued to hospitals and health providers were discarded (National Blood Authority 2014). Any change to recommendations for individual patients must therefore take account of the effect on the global blood supply. For example, if ICU patients derive benefit from receiving the freshest possible red cells, what effect will this have on other trauma patients? If 1:1:1 is optimal in massive transfusion, what are the implications for plasma supply to other patients? These questions will almost certainly confront blood service managers in the near future.

Patient Blood Management (PBM)

PBM aims to reduce “unnecessary” exposure to blood components. An audit of ten Australian hospitals found 35% of red cell transfusion episodes included inappropriate units (defined by similar criteria to those of PBM) (Rubin et al. 2000). PBM is a rational response to both the new “evidence-based” paradigm in blood transfusion, and a means of conserving the blood supply. Adopting PBM must itself be evaluated, ideally through prospective registries such as the massive transfusion registry of the Australian Blood Centre of Research Excellence (http://www.anzicrc.monash.org/blood-cre.html).

Conclusion

Renewed interest in blood product resuscitation for major trauma has occurred in the era of evidence-based medicine. Existing therapies are currently the subject of effectiveness trials that will impact both individual patient management and that of the blood supply. While existing blood products became established in practice largely on the basis of anecdote, theory, and absence of immediate adverse effects, the evidence required of new or alternative therapies is comparable to that of pharmaceuticals. Regulators must balance caution with innovation in what has, until recently, been an evidence-free field.

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