Hemodynamic Resuscitation: What is PROPPR?

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Article:
Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 ratio and mortality in patients with severe trauma. The PROPPR randomized clinical trial. JAMA. 2015;313:471-482

February 2015 marked the long-awaited publication of the (PROPPR) trial in the Journal of the American Medical Association.[1] This is a landmark study for traumatologists of any discipline, because it provides evidence to answer a key question in resuscitation during active hemorrhage: What blood products should we administer?

The tenets of damage control (or hemostatic) resuscitation have been published frequently:[2]

- Rapid diagnosis of hemorrhagic shock and active bleeding
- Rapid definitive anatomic control (operating room or angiography)
- Surgery focused on control of hemorrhage, with deferral of definitive repairs
- Deliberate hypotension during active hemorrhage
- Early administration of an antifibrinolytic agent
- Maintenance of core body temperature
- A massive transfusion protocol designed to speed the arrival of blood products to the bedside
- Early administration of plasma and platelets

Of these recommendations, the last has been the most controversial and the hardest to substantiate with scientific evidence. In the Vietnam era, most transfusions were with whole blood. In the 1980s and 90s this practice changed to a component-based approach, with plasma or platelet administration reserved for patients with laboratory evidence of coagulopathy. While this practice served most patients well, by limiting exposure to unneeded elements, it left something to be desired in severely injured trauma patients. This population was both highly dynamic – often bleeding faster than lab tests could be turned around – and suffering from a combined deficiency of multiple components. By the turn of the millennium the deficiencies of component-based resuscitation were becoming obvious to trauma-focused clinicians. This was especially true as resuscitation improved in other areas with the advent of improved intravenous access, efficient high-volume fluid warmers, damage-control surgical techniques, deliberate hypotension, fibrin sealants and the like. The pragmatic clinical answer was administration of 'simulated' whole blood using a 1:1:1 ratio of plasma to platelets to red blood cells (RBC) in patients at high risk for exsanguination.

Diffusion of this approach within the trauma community was accelerated by the US entry into the global war on terror. The need to care for military and civilian casualties at risk for massive hemorrhage under relatively austere conditions led to search for new and better approaches to resuscitation, including the idea of 1:1:1 transfusion. Analysis of retrospective data from military and civilian hospitals demonstrated a substantial benefit to survival associated with administration of larger quantities of plasma, but was unfortunately contaminated by survival bias.[3] The most badly injured and rapidly hemorrhaging patients had a high risk of dying after receiving RBC but before plasma reached the bedside. More sophisticated retrospective studies which attempted to control for this effect were not as likely to demonstrate a benefit, although some succeeded.[4] Controversy followed, along with the obvious need for a prospective trial. Thus was PROPPR born.

Under the estimable direction of Dr. John Holcomb of the University of Texas, Houston, 12 major centers combined to enroll 680 actively hemorrhaging trauma patients in a prospective randomized trial of 1:1:1 vs. 1:1:2 transfusion (plasma to platelets to RBC). Other than transfusing blood products in a pre-specified order, all other aspects of trauma care were left to the standards of the individual centers. The study was conducted using a waiver from prospective informed consent. Enrollment was based on either active transfusion (between 1-3 units) at the time of admission or a high risk for massive transfusion. Protocolized transfusion was continued until the patient died or effective surgical or angiographic hemostasis was achieved. Protocol adherence was quite good, with few patients lost to follow-up. Study results were consistent with expectations, but frustratingly non-definitive. Patients in the 1:1:1 cohort were less likely to die of exsanguination in the first 24 hours (9.2% vs. 14.6%, $p = 0.03$) and more likely to achieve hemostasis (86.1% vs. 78.1%, $p = 0.06$), but differences in overall 24-hour (12.7% vs. 17.0%, $p = 0.12$) and 30-day (22.4% vs. 26.1%, $p = 0.26$) mortality were not significantly different.

So what should the traumatologist conclude? One interpretation would be that 1:1:1 transfusion reduces the chance of dying in the short-term, before anatomic control of bleeding is achieved, while mildly increasing the risk of dying in the long-term, due to the negative immune consequences of greater volumes of plasma and platelets. The fact that the researchers could not identify a discreet clinical outcome that was different between the groups following resuscitation – despite examining more than two dozen candidates – illustrates just how subtle the negative consequences of plasma may be in the chaos of trauma resuscitation.

To this experienced observer, the results of PROPPR provide convincing evidence in support of 1:1:1 resuscitation, at least during early care when decisions must be made in the absence of diagnostic certainty. The heterogeneity of trauma patients makes any large clinical trial something of an adventure, and will always make it hard to separate noise from signal in clinical studies. Despite attempted exclusion, more than 1/3 of the deaths in each group were due to traumatic brain injury rather than hemorrhage. While PROPPR did not demonstrate a significant difference in mortality it at least suggests no large negatives associated with the 1:1:1 approach, despite giving larger volumes of plasma and platelets. 1:1:1 resuscitation improves short term survival, and creates the chance to “live to fight another day.”

References

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