CME

What Is the PROPPR Transfusion Strategy in Trauma Resuscitation?

Gregory M. Janelle, MD, FASE,* Linda Shore-Lesserson, MD, FAHA, FASE,† Charles E. Smith, MD,‡ Jerrold H. Levy, MD, FAHA, FCCM,§‖ and Aryeh Shander, MD, FCCP, FCCM¶

A massive transfusion protocol is increasingly used in trauma patients. However, the ideal ratio of plasma to other factors has been the subject of significant debate.[1–5] The current published data and clinical practice are based primarily on retrospective database analyses. The Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial,[6] the largest multicentered prospective randomized controlled trial to date, compared outcomes in hemorrhaging trauma patients with a 1:1:1 ratio of plasma, platelets, and red blood cells versus a 1:1:2 ratio. Although no mortality difference was found, patients in the 1:1:1 group had fewer deaths from exsanguination and improved hemostasis. The authors of the PROPPR trial have interpreted their findings as favoring a 1:1:1 ratio of plasma, platelets, and red blood cells as the key resuscitative formula in massively hemorrhaging patients when compared with a 1:1:2 ratio. However, we believe that a critical examination of the methodology and conclusions necessitates cautious interpretation of these results.

The rationale behind early massive transfusion protocols such as those tested in the PROPPR trial is to rapidly provide blood products in the face of time pressure and clinical uncertainty regarding the extent and future duration of severe bleeding. Ratio-based transfusion is not intended to replace transfusion based on coagulation testing but rather to supplement it with the goal of more effective control of acute trauma coagulopathy and hemorrhagic shock. However, acute trauma coagulopathy is a multifactorial process often initiated by shock-induced tissue hypoperfusion and injury and exacerbated by hypothermia, acidemia, and dilutional coagulopathy after infusion of fluids and blood components.[7] Given the multifactorial etiology, preset ratios of blood components may thus have a limited ability to address all types of acute trauma coagulopathy. Fibrinogen is often the first coagulation factor that declines to critical levels in massive bleeding, yet the fibrinogen content of plasma is relatively low compared with cryoprecipitate; therefore, fresh frozen plasma and/or thawed plasma are likely not the best choices for fibrinogen replacement.[7,8] Furthermore, studies suggest that a ratio of red blood cells to plasma units varying from 1:1 to 1:2 does not improve rotational thromboelastometry-based coagulation measurements in trauma patients and is not a patient-driven approach.[9] Therefore, a ratio-driven transfusion protocol is unlikely to accurately address hemostatic requirements in a hemorrhaging patient.

According to prepublication descriptions of the PROPPR design and implementation,[10] the study was undertaken primarily to investigate whether in-hospital death from massive truncal hemorrhage could be reduced when a 1:1:1 transfusion ratio was used to achieve rapid hemorrhage control. The hypothesis was that improved resuscitation techniques such as a 1:1:1 ratio and earlier use of platelets would prevent and treat coagulopathy, minimize the use crystalloid fluids, and improve survival. The tenets of hemostatic resuscitation using a massive transfusion protocol permit early mobilization of resources, including blood products, thus reducing logistic barriers to effective care. However, rapid anatomic control of bleeding (e.g., primary surgical hemostasis) is often the most influential factor for survival. Thus, if rapid surgical hemostasis is obtained, should one expect that the early fixed ratio administration of platelets and plasma will have any appreciable effect on fluid management and outcome? This direct effect of surgical hemostasis on outcome may have played a role in the PROPPR results. Both study groups had a similarly small occurrence of massive transfusion, defined as at least 10 units of packed red blood cells in the first 24 hours. If less than one-half of patients receive a massive transfusion (45% of the 1:1:1 group versus 47% of the 1:1:2 group), is it logical to expect a difference in outcomes related to massive transfusion protocols? The inclusion criteria for the study consisted of 2 or more Assessment of Blood Consumption (ABC) criteria that, according to previously published reports, have a sensitivity of 75% to 90% and a specificity of 67% to 88% for determining who will require a massive transfusion.[11,12] An alternative inclusion criterion was the perceived need for massive transfusion, but these combined criteria inaccurately predicted massive transfusion in >50% of patients in the PROPPR trial. Although this rate of massive transfusion is comparable to other prospective, randomized trauma trials such as CONTROL and CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant

From the *Department of Anesthesiology, University of Florida, Gainesville, Florida; †Department of Anesthesiology, Hofstra Northshore-LIJ School of Medicine, Hempstead, New York; ‡Department of Anesthesiology, Case Western Reserve University, Cleveland, Ohio; Departments of §Anesthesiology and ‖Surgery, Duke University, Durham, North Carolina; and ¶Department of Anesthesiology, Englewood Hospital and Medical Center, Englewood, New Jersey.

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Address correspondence to Gregory M. Janelle, MD, FASE, Department of Anesthesiology, University of Florida, 1600 SW Archer Rd., P.O. Box 100254, Gainesville, FL 32610. Address e-mail to gjanelle@anest.ufl.edu.

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Haemorrhage),[13,14] frontline physicians cannot predict with certainty those patients who will require a massive transfusion and those in whom the surgeon will obtain early control of bleeding. A post hoc analysis of any mortality differences that may have existed in the studied patients who actually did require massive transfusion would help to clarify the effect of transfusion ratios per se.

The randomization protocol in the PROPPR study also dictated methodologic differences in product administration beyond that calculated by a difference in resuscitative formulas. Although the ratio of red blood cells to plasma was targeted as the major independent variable, the study methodology dictated that the 1:1:1 group would receive platelets in the initial container sent for the first "round" of transfusion, whereas the 1:1:2 group would receive no platelets in the initial container. Because each unit of pooled platelets was counted as 6 units, everyone in the 1:1:1 group received 6 units of platelets along with the first 6 units of packed red blood cells. In contrast, subjects randomly assigned to the 1:1:2 group who received 9 units of products or less (6 units red blood cells + 3 units plasma) never received platelets at all. By protocol, therefore, patients randomly assigned to the 1:1:2 group would only receive platelets when >9 units of products were administered. This variance necessarily introduced a serious confounder, especially if one includes the volume of plasma given with platelets. This asymmetry in platelet administration between groups can be seen clearly in the results of the PROPPR trial, which reported a median platelet dose of 12 units in the 1:1:1 group but only 6 in the 1:1:2 group ($P < 0.001$). The plasma difference between the groups (median of 7 vs 5, respectively) was also statistically significant because the 1:1:1 group should have received 1 unit of plasma for every 3 units of product versus 1 unit of every 4 in the 1:1:2 group.

In the light of these methodologic limitations, it is important to understand that the median number of transfused red blood cell units did not differ between groups, causing the reader to question whether or not improved hemostasis in the 1:1:1 group was clinically significant. In addition, based on median units transfused, the ratios administered to the 1:1:1 and 1:1:2 groups calculate to 1:1.7:1.3 versus 1:1.2:1.8, respectively, further leading the reader to wonder if the target ratios were actually achieved. Although the median total blood products were the same between the 1:1:1 group and the 1:1:2 group (15 vs 14 units) during the intervention period, patients in the 1:1:2 group received less overall product in 24 hours (19 units) versus the 1:1:1 group (25.5 units).

Because there were no differences in mortality between groups, the only positive study outcomes were differences in hemostasis achieved and in death because of exsanguination by 24 hours. Of note, the prespecified clinically meaningful difference in mortality was set at 10%, and death from exsanguination was not mentioned in any of the stated hypotheses or ancillary clinical aims.[10] Hemostasis, as judged by unblinded surgeons, was statistically better in the 1:1:1 group, with an absolute difference of 8% (86.1% in 1:1:1 vs 78.1% in 1:1:2). Death from exsanguination differed in the first 24 hours by 5.4% (9.2% in 1:1:1 vs 14.6% in 1:1:2). However, because the median time to mortality from exsanguination was 2.3 hours in the study, it may be misleading to suggest that the resuscitation ratio played a significant role in the creation of hemostasis within this time period. Rather, unexpected differences in the number of survivable injuries may have been present between groups. One could instead infer that if patients did not succumb to early exsanguination from failed surgical control of hemorrhage, primary or secondary 24-hour outcomes would not differ between groups. Because data on anatomic injuries and their severity are not reported, we cannot determine the relative impact of early exsanguination or hemostasis between groups. It is noteworthy that the one transfusion-related mortality was in the 1:1:1 group and attributed to transfusion-associated circulatory overload, a potentially avoidable death. Although the death happened outside the first 24 hours, it is not clear whether this patient actually experienced massive hemorrhage and/or whether the death was a consequence of the products issued during the study.

Another critical consideration is that cryoprecipitate administration in the PROPPR study was not controlled. Significant differences were reported in cryoprecipitate use between groups, with the 1:1:2 group receiving more cryoprecipitate. Initial laboratory data demonstrated that only approximately 25% of patients had evidence of even mild coagulopathy (international normalized ratio >1.5 or TEG® [Hemoscope Corp., Niles, IL] r value > 8 minutes), and none had evidence of fibrinogen dysfunction or deficiency. No explanation is available for the variable cryoprecipitate administration to study groups with injuries perceived (although not reported) to be comparable. Such a difference in cryoprecipitate administration is clinically relevant because fibrinogen rapidly declines and fibrinolysis starts within 15 minutes of major blunt trauma. The Prehospital Air Medical Plasma (PAMPer) trial, among others, strongly suggests that fresh frozen plasma and cryoprecipitate should be started by first responders.[15]

The PROPPR trial did demonstrate that early hemostatic intervention is important in a portion of severely injured patients. All the health care teams caring for severe trauma patients at the 12 participating centers are to be commended for a lower than predicted mortality rate from major trauma when compared with historic controls. Although patients in both arms of the PROPPR study had outcomes substantially better than previous research cohorts, additional unreported results that would aid interpretation are the outcomes in the patients who actually required massive transfusion but survived early exsanguination and if there were any differences as a result of different transfusion protocols. Also not reported in this article are the point-of-care assays that may have been available when the injured patients were presented. Information from these assays may have helped to guide targeted and specific hemostatic therapy without the need for an empiric transfusion ratio.

Another limitation of the PROPPR study is that blood pressure management was not addressed. The absence of information on blood pressure management in the PROPPR study also limits its generalizability to all trauma patients. Although theoretically lower mean arterial blood pressures may be useful in decreasing potential bleeding, this strategy may worsen outcomes in patients with severe head

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injuries.[16,17] Furthermore, hypotension and lower blood pressures may also indicate uncontrolled shock that itself is associated with worse outcomes. In addition, because PROPPR subjects were >75% men approximately 34 years of age, clinicians should be cautious in applying these findings to major obstetrical, gastrointestinal, or postcardiotomy hemorrhage.

Despite the above limitations, the authors and numerous institutions involved in the PROPPR trial are to be congratulated on their concentrated efforts to study an extremely difficult clinical question in the challenging environment of acute trauma resuscitation. Emergency research with an exception from informed consent, community consultation, and public disclosure are important and often costly considerations that are needed before study initiation.[18] Appropriate study end points, trauma epidemiology (e.g., heterogeneous patients with heterogeneous injuries), patient enrollment, and inclusion criteria are also critical in the success of emergency research in trauma care.[19] The PROPPR investigators identified clear, unambiguous end points (such as 24-hour and 30-day mortality), performed external data and safety monitoring, navigated a difficult consent issue, using exception from informed consent but performing community consultation with delayed patient or legally authorized representative consent. Finally, funding a 680-patient, multicenter study that uses no proprietary device or pharmaceutical is a major accomplishment.

As the medical community struggles to improve local practice and outcomes, we caution providers to avoid the temptation to pool multitrauma patients into an algorithmic treatment plan rather than using well-described patient-centered therapies. Rather than focusing our efforts on finding an ideal resuscitative transfusion formula, we advocate continuous reassessment of ongoing hemostasis changes in individual patients guided by point-of-care coagulation monitoring. This approach turns the massive "transfusion" protocol into a massive "hemorrhage" protocol. The indications and end point of plasma use, platelet administration, and cryoprecipitate could perhaps be better guided by viscoelastic testing than by empiric formulas. Holcomb et al.[20] suggest that point-of-care testing using thromboelastography predicts transfusion needs and correlates with mortality. Another dose-guided algorithm for use in trauma patients has been suggested by Johansson et al.,[5] which indicates a dose of transfusion therapy that is graded to the degree of hemostatic impairment. Tapia et al.[21] have used point-of-care viscoelastic testing in an algorithmic fashion for determining transfusion therapy for trauma patients. Using a before-after design, Tapia et al. found that point-of-care testing resulted in less plasma transfusion in blunt trauma patients receiving >6 units of red blood cells, but no difference in mortality. In patients with penetrating trauma receiving >10 units of red blood cell transfusion, the point-of-care group had a significantly lower mortality.[21] This concept is also supported in a pediatric cardiac study published by Nakayama et al.[22] where only platelets and plasma were available as hemostatic components. Thus, one is left to surmise about the necessity of either 1:1:1 or 1:1:2 in some patients who could have perhaps been more conservatively managed with strategies using crystalloid, colloid, and/or factor concentrates.

In massive trauma, we believe clinicians should seek patient-specific therapies and not pool patients into a one-size-fits-all treatment plan. Overall, ratio-based transfusion is not intended to replace coagulation test-guided care but rather to supplement it in the face of time pressure or clinical uncertainty regarding the extent and future duration of hemorrhage. Point-of-care/laboratory-guided precision resuscitation is the theoretically optimal choice if the results are obtained rapidly, and the necessary blood products and/or pharmacologic treatments are immediately available. The clinical reality is that we have yet to achieve this goal. Rapid, ratio-based delivery of products to the bedside is one reason that patients in both arms of the PROPPR trial had lower than expected mortality. We advocate continuous reassessment of ongoing changes in individual patients guided by point-of-care coagulation monitoring and individualized hemodynamic monitoring.[21–24] Rather than focusing on the application of a massive transfusion protocol, it may be more appropriate for clinicians to focus on a massive hemorrhage protocol that addresses patient-specific factors, source control of bleeding, hemostatic monitoring, and the optimization of relevant physiologic parameters.

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Name: Charles E. Smith, MD.
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