Published in final edited form as:

Surgery. 2016 December ; 160(6): 1560–1567. doi:10.1016/j.surg.2016.05.022.

To be considered for publication in the Journal, *Surgery*: Ideal Hemoglobin Transfusion Target for Resuscitation of Massive Transfusion Patients

Martin D. Zielinski, MD, Gregory A. Wilson, RRT, Pamela M. Johnson, Stephanie F. Polites, MD, Donald H. Jenkins, MD, W. Scott Harmsen, MD, John B. Holcomb, MD, Charles E. Wade, PhD, Deborah J. Del Junco, PhD, Erin E. Fox, PhD, and James R. Stubbs, MD

Abstract

Background—Over-transfusion (OT) of packed red blood cells (pRBCs) is known to increase the risk of death in stable patients. With the delineation of minimum transfusion ratios in hemorrhaging patients complete, attention must be turned to the other end of the massive transfusion (MT) spectrum, that of defining the maximum transfusion of pRBCs. We aimed to define the ideal HgB range 24 hours after anatomic hemostasis associated with the lowest mortality.

Study Design and Methods—MT patients (≥ 10 units pRBCs within 24 hours) were reviewed from 2010–2013. The hemoglobin (HgB) 24 $\pm$ 6 hours after anatomic hemostasis was used to stratify patients into under-transfusion (UT; <8.0), hemoglobin transfusion target (HTT; 8.0–11.9), and OT (>12.0 g/dL) groups; patients not surviving to 24 hours were excluded.

Results—We identified 418 patients (351 HTT [84%], 38 UT [9%], and 29 OT [7%]) with an overall mortality of 18%. UT patients had the greatest risk of death (OR 3.3; 95% CI 1.6–6.7) followed by OT patients (OR 2.5; 95% CI 1.1–5.6). Though pre-transfusion HgB was similar (9.5 ± 2.2 vs 9.5 ± 2.3 g/dL), OT patients had greater HgB values during MT (8.3 ± 3.0 vs 6.9 ± 1.4

Address correspondence to: Dr. Martin D. Zielinski, Division of Trauma, Critical Care and General Surgery, Mary Brigh 2-810, St. Mary's Hospital, Mayo Clinic, 1216 Second St. SW, Rochester, MN 55902, Phone: (507) 255-2923, Fax: (507) 255-9872, zielinski.martin@mayo.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

The authors declare that they have no conflicts of interest relevant to the manuscript submitted to the Journal, *Surgery*.

AUTHOR CONTRIBUTIONS

MARTIN D. ZIELINSKI, MD – PRIMARY INVESTIGATOR, GRANT AWARD WINNER, PROJECT DEVELOPMENT AND IMPLEMENTATION, MANUSCRIPT PREPERATION AND EDITING

GREGORY A. WILSON, RRT – DATA COLLECTION, DATA ANALYSIS, MANUSCRIPT EDITING

PAMELA M. JOHNSON – DATA COLLECTION, DATA ANALYSIS, MANUSCRIPT EDITING

STEPHANIE F. POLITES, MD - DATA COLLECTION, DATA ANALYSIS, MANUSCRIPT EDITING

DONALD JENKINS, MD – PROJECT DEVELOPMENT, GRANT MENTOR, MANUSCRIPT EDITING

W. SCOTT HARMSSEN, MS – DATA ANALYSIS, MANUSCRIPT EDITING

JOHN B. HOLCOMB, MD – PROJECT DEVELOPMENT, MANUSCRIPT EDITING

CHARLES E. WADE, PHD - PROJECT DEVELOPMENT, MANUSCRIPT EDITING

DEBORAH J. DEL JUNCO, PHD - PROJECT DEVELOPMENT, MANUSCRIPT EDITING

ERIN E. FOX, PH.D - PROJECT DEVELOPMENT, MANUSCRIPT EDITING

JAMES R. STUBBS, MD - PROJECT DEVELOPMENT, GRANT MENTOR, MANUSCRIPT EDITING

g/dL) persisting until hospital dismissal/death (11.4 ± 2.3 vs 9.6 ± 1.1 g/dL). In total, 657.4 excess pRBC units were transfused (1.9 ± 1.5 per patient).

Conclusion—OT patients had increased mortality, comparable to UT patients, despite younger age and fewer comorbidities. Shorter MT durations foster a scenario in which patients are at greater risk of OT.

INTRODUCTION

Packed Red Blood Cell (pRBC) transfusions are a double edged sword; they are both life-saving and cause harm. They cause transfusion-associated acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), and increase the risk, in a dose dependent manner, of infection, immunosuppression, wound complications, multisystem organ failure, and death.^{1,2,3} In fact, the risk of death associated with pRBC over-transfusion (OT) is increased by nearly 50% in critically ill, but non-hemorrhaging, patients.⁴ As a result of this harm, restrictive hemoglobin (Hgb) transfusion triggers have been identified and confirmed to reduce mortality.⁵ Due to the rapid nature of hemorrhage resuscitation, however, waiting for laboratory test results to return is not possible as the patient's current degree of anemia will not be represented by the delayed Hgb value. Hgb transfusion triggers, therefore, have limited applicability during hemorrhage resuscitation.⁶ Instead, massive transfusion (MT; 10 pRBC units in 24 hours) resuscitation relies on the proactive transfusion of pRBC, plasma, and platelets in equal ratios with one another with little initial regard to lab values.^{7,8} This approach has been successful in avoiding pRBC under-transfusion (UT) but little consideration to pRBC OT has been given or reported.

While Hgb transfusion triggers effectively guide the initiation of a pRBC transfusion in stable, non-hemorrhaging patients, a different solution for MT patients must be created. A potential solution may lie in the identification of a Hgb target associated with the least odds of death after resuscitation has been completed and the patient's vascular space has equilibrated. This method allows for the simultaneous consideration of pRBC OT and UT. Unfortunately, we do not know the definition of pRBC OT in MT patients. The aim of this study, therefore, is to define pRBC OT and identify the ideal Hgb range 24 hours after anatomic hemostasis that is associated with the lowest mortality in MT patients. Additionally, we will identify clinical features associated with increased risk of OT during MT.

METHODS

Institutional review board approval was obtained to review the medical records of surgical and trauma patients who underwent MT between 2010 and 2013 at a single institution. Patients who underwent cardiac surgery or required cardiopulmonary bypass were excluded. The Hgb value obtained 24 ± 6 hours after anatomic hemostasis, defined as the time point of the last (tenth or higher) consecutive pRBC transfusion followed by no pRBC transfusions for at least 6 hours, was used to stratify patients; patients who died prior to this time were excluded. The 24-hour time point for stratification was chosen a priori by group consensus. Our rationale was to ensure sufficient time for redistribution of fluid between the vascular and intestinal/cellular spaces and to accurately identify patients with persistent hemorrhage.

Point of care HgB tests were not considered for the HgB stratification due to the differing values and margins of error. The critical administration threshold (CAT), an alternative massive transfusion definition, was defined as 3 units pRBC in 60 minutes anytime within 24 hours of ED admission.

The odds of mortality (independent variable) were plotted in comparison to the HgB value 24 ± 6 hours after anatomic hemostasis (dependent variable). pRBC OT was defined as the HgB value threshold above which an inflection was present for increased mortality. Similarly, pRBC UT was defined as the lowest HgB inflection value below which mortality increased. These high and low inflection points would thus define of the ideal HgB range associated with the lowest mortality. The duration of transfusion was defined as the amount of time elapsed from the initial pRBC transfusion through anatomic hemostasis. Given the multiple independent ARDS risk factors present in every patient, all diagnoses of ARDS were considered as possible TRALI.⁹

Our institution has had a MT protocol in place since 2008 which emphasizes the use of 1:1:2 – 1:1:1 blood product resuscitation in conjunction with thromboelastogram driven resuscitation for reversal of coagulopathy. This protocol was consistent throughout the study period. The protocol, however, did not call for specific timing of HgB testing.

Statistical Analysis

Mortality was compared between OT, reference, and UT cohorts using analysis of variance (ANOVA) followed by equal variance T-tests and Chi-square analyses as appropriate when ANOVA was significant. The odds of death were controlled for using the clinically significant variables of age, sex, and Charlson Comorbidity Score using multivariable linear regression. Features independently associated with pRBC OT were determined using multivariable logistic regression analysis. The features with the lowest p-values were included. Data are presented as means ± standard deviations with a p<0.05 considered statistically significant.

RESULTS

In total, 547 MT patients survived to the 24 hour time point of whom 129 were excluded due to undergoing cardiac surgery or cardiopulmonary bypass. Therefore, 418 patients were included in the analysis. The cohort was heterogeneous made up of 39% general surgery, 13% trauma, 12% spine, 9% vascular, 8% liver transplant, 6% orthopedics, 5% urology, 3% non-cardiac thoracic, 3% oral-maxillofacial, 2% neurosurgery, and 0.3% kidney/pancreas transplant patients.

Overall in-hospital mortality was 18%. The odds of mortality increased above 12.0 g/dL (pRBC OT) while the lower inflection point was below 8.0 g/dL after controlling for potential confounders (pRBC UT; Figure 1, Table 2). There was a suggestion of increased mortality in the 10.0 g/dL or greater range (OR 1.4, 95% CI 0.78–2.5) compared to 8.0 – 9.9 g/dL, but statistical significance was not reached until the 12.0 g/dL or greater. Therefore, the ideal HgB range was defined as 8.0–11.9 g/dL (reference cohort). These three ranges provided the cohorts for the remainder of the analysis. The most common causes of death

were exsanguination in the UT cohort (82%), multisystem organ failure (53%) in the reference cohort, and traumatic brain injury (40%) in the OT cohort.

There were 351 patients in the reference cohort (84%), 38 in the UT cohort (9%), and 29 in the OT cohort (7%). UT patients had the greatest risk of in-hospital death (OR 3.3; 95% CI 1.6–6.7) closely followed by OT patients (OR 2.5; 95% CI 1.1–5.6) when compared to the reference cohort. Each cohort had similar rates of trauma patients distributed among them; over transfusion 35.3%, UT 41.2% and reference 22.1% ($p=.14$). There was no difference in mortality in trauma versus non-trauma surgical patients (25.0% vs 25.2%, $p>.99$).

pRBC OT versus Reference Cohort Comparison

Comparison of OT patients to the reference group demonstrated that they were younger (49.8 ± 22.8 vs 57.9 ± 16.7 years; $p=.02$) and healthier (Charlson Comorbidity Score 2.9 ± 2.7 vs 4.9 ± 3.2 , $p=.002$) but with similar HgB values prior to the initiation of MT (9.5 ± 2.2 vs 9.5 ± 2.3 g/dL, $p=.88$). The OT patients received similar volumes of blood products in 24 hours as the reference cohort; pRBCs (18 ± 10 vs 21 ± 13 units; $p=.34$), plasma (12.7 ± 6.5 vs 10.8 ± 9.4 units; $p=.291$), and platelets (3.4 ± 2.9 vs 4.2 ± 3.7 units; $p=.24$). The OT patients had a greater plasma to pRBC ratio at 24 hours than the UT and HTT patients (0.74:1 vs. 0.56:1 vs 0.50:1, respectively; $p<.001$). There were no differences in the platelet to pRBC ratio, however (0.17:1 vs. 0.19:1 vs 0.20:1; $p=.439$). OT patients received lower volumes of non-blood colloid (1.90 ± 2.69 vs. 3.33 ± 3.09 L; $p=.015$) but similar volumes of crystalloid (9.73 ± 6.77 L vs. 11.95 ± 7.01 L; $p=.10$) in 24 hours. Despite similar baseline HgB values (9.5 ± 2.2 vs 9.5 ± 2.3 g/dL) and receiving similar volumes of pRBC, the minimum HgB value during MT was greater in OT patients (8.3 ± 3.0 vs 6.9 ± 1.4 g/dL; $p<.001$) which persisted through hospital dismissal or death (11.4 ± 2.3 vs 9.6 ± 1.1 g/dL; $p<.001$). The rate of CAT was similar between the two cohorts (88% vs 89%, $p=.93$). The OT patients had a significantly shorter duration of transfusion (14.1 ± 13.6 vs 27.0 ± 18.4 hours; $p<.001$) than the reference cohort. Additionally, OT patients were more tachycardic (129 ± 23 vs. 114 ± 28 beats per minute, $p=.004$) but were less hypotensive during the MT event (systolic blood pressure 73.7 ± 41.8 vs. 60.5 ± 18.1 mm Hg; $p=.001$). The lowest recorded PaO₂/FiO₂ ratio during the first 7 days after MT were similar (163.3 ± 110.6 vs. 169.4 ± 96.9 ; $p=.75$) as were the durations of ventilator days (6.4 ± 7.4 vs. 6.3 ± 10.6 days; $p=.78$).

Multivariable analysis demonstrated that age less than 40 years and recorded systolic blood pressure (SBP) less than 50 mm Hg or greater than 70 mm Hg during MT were independently associated with pRBC OT (Table 3, Figures 2 and 3).

Assuming all patients with HgB >8.0 g/dL at 24 ± 6 hours after anatomic hemostasis could have been transfused to the lowest possible HgB value in the ideal HgB range (i.e. 8.0 g/dL) and that 1 unit of pRBC was equivalent to 1.0 g/dL, 1.9 ± 1.5 additional pRBC units were transfused per patient. In total for all of the patients, 657.4 excess units were transfused.

DISCUSSION

The results of the manuscript represent an initial attempt at defining optimal blood product transfusion practice for hemorrhage resuscitation. HgB values between 8.0 and 11.9 g/dL 24

hours after anatomic hemostasis provided the lowest odds of death in massively hemorrhaging patients when controlled for potential confounders. Not surprisingly, UT patients had the greatest mortality odds but, more significantly, the data demonstrated that OT patients had substantially increased odds of death which approached the odds of death of UT patients. Therefore, we defined pRBC OT as HgB value 12.0 g/dL or greater 24 hours after anatomic hemostasis.

The notion that OT of pRBCs causes harm is not novel. Restrictive HgB transfusion triggers were developed to prevent pRBC OT and their unintended consequences. These triggers, by allowing for the laboratory-guided management of anemia in critically ill non-hemorrhaging patients, signify the point where the risks of complications from untreated critical anemia are greater than the risks of complications from pRBC transfusions.^{4,10} The applicability of HgB transfusion triggers to MT patients is limited, however. The most current recommendations for pRBC transfusions in trauma patients is for a HgB trigger <7.0 g/dL but only in hemodynamically stable patients “after the acute resuscitation phase has been completed.”⁶ This expert recommendation is based on a subgroup analysis of trauma patients from the Transfusion in Critical Care (TRICC) randomized controlled trial comparing liberal (<10.0 g/dL) versus restrictive (<7.0 g/dL) transfusion triggers. Despite having 100 patients in the restrictive and 103 in the liberal cohorts, the authors concluded that “these studies were insufficiently powered to address the influence of different transfusion strategies on clinically important outcomes for trauma patients.”¹¹

Only one study has looked at HgB transfusion triggers in actively hemorrhaging patients. Villanueva et al studied restrictive (<7 g/dL) versus liberal (<9 g/dL) HgB transfusion triggers in a randomized clinical trial of patients being treated with endoscopy for upper gastrointestinal bleeding.¹² There was a significant improvement in survival at 6 weeks in those patients who were randomized to the restrictive cohort (95% vs 91%, $p=.02$). Additionally, these patients had fewer re-bleeding episodes (10% vs 16%, $p=.01$). While this study indeed focused on bleeding patients, their population was a substantial departure from hemorrhaging trauma patients; “massive exsanguination” patients were excluded. While the definition of massive exsanguination was not mentioned, presumably all of the patients in our study, by virtue of meeting MT threshold, would have far exceeded the volume of blood loss for inclusion. In fact, the volumes of pRBCs transfused in their study were relatively minimal with 1.5 ± 2.3 units in the restrictive cohort and 3.7 ± 3.8 units in the liberal cohort. The reason for the exclusion of patients with substantial hemorrhage in these studies is the uncertainty of the degree of anemia and the inability to rely on a HgB transfusion trigger. Outside of cardiac surgery, attempts at restrictive strategies do not exist for acutely unstable, hemorrhaging patients.^{13,14,15}

The ideal HgB range identified in this study was broad with an unexpectedly high HgB OT definition. In the majority of clinical trials, the most common HgB transfusion triggers are 7.0 g/dL or 8.0 g/dL in the restrictive arms and 9.0 g/dL or 10.0 g/dL in the liberal arms.^{4,15} These values are substantially lower than our identified pRBC OT definition. It must be remembered, however, that these trigger values denote the initiation of a pRBC transfusion while the range identified in this study is a target to aim for after transfusion has begun. In other words, the difference in practice between transfusing hemorrhaging versus non-

hemorrhaging patients is aiming for a target range rather than a relying on a trigger. Transfusion into this ideal range, however, will likely prove difficult until a valid method exists to determine the HgB target value, in real time, for patients in hemorrhagic shock.

The 24 hour time point after anatomic hemostasis was selected for two primary reasons. First, a sufficient duration of time must elapse to ensure patients are no longer hemorrhaging. The Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial had very specific definitions for anatomic hemostasis.⁷ As a retrospective study, however, we could not rely on these prospectively defined time points. Instead, our definition of anatomic hemostasis incorporated a minimum duration of time elapsing in which no units of pRBCs were transfused. Second, a sufficient duration of time must have elapsed between the last pRBC transfusion and the equilibration of the intra/extracellular and intra-vascular spaces in order to as accurately as possible reflect the patient's true red cell mass. The minimum sufficient duration of time required for this equilibrium to occur is difficult to assess as the magnitude of fluid shifts into the third space are poorly described and difficult to accurately assess.¹⁶ Prospective evaluation will allow the determination of whether a HgB value drawn at an earlier time point after anatomic hemostasis, but before the 24-hour mark, is even more strongly associated with increased odds of death.

The pRBC OT definition is based on a HgB reached after conclusion of the MT event. Clinicians must be able to predict who is at risk for OT ahead of time. Of the three identified risk factors, only age less than 40 is known at the onset of hemorrhage. We suspect that the risk factor of younger age may be due to these patients' enhanced ability to compensate for a limited preload until their cardiovascular system can no longer compensate for profound hypovolemia which consequently forces clinicians to aggressively transfuse. The remaining two features, both based on SBP, could be present throughout the resuscitation phase. Severe hypotension as a risk factor for pRBC OT is likely caused by a torrent of blood product administration during the hypotension episode which may not have been necessary. Alternatively, unbalanced resuscitation ratios of plasma to pRBCs may result in more pRBCs being transfused with a consequently elevated HgB value. Conversely, a recorded lowest SBP greater than 70 may be a function of a lack of permissive hypotension breaking the present, but fragile, thrombi at the points of hemorrhage creating further bleeding.¹⁷ Unfortunately, power limited our ability to discern any additional multivariable features. Based on univariate analysis, however, a shorter duration of resuscitation was associated with pRBC OT. Likely, less time allowed fewer labs draws, including HgB values, to help drive resuscitation. Instead of predictive clinical features, technological adjuncts such as non-invasive HgB monitors may be a solution to guide MT and avoid OT.^{18,19}

While there was a suggestion of greater mortality in the patients who reached 10.0 g/dL or greater, significance was not reached until 12.0 g/dL. We suspect there is a blood loss threshold lower than MT that still provides a significant risk for pRBC OT but with lower risk for death from exsanguination. Additionally, there was a relatively rapid increase in the odds of mortality for patients with a HgB less than 8.0 g/dL. Whether targeting this range, or perhaps a narrower one, during the resuscitation of hemorrhaging patients will affect mortality requires further study.

This was an initial attempt at defining a target, rather than trigger, to guide pRBC transfusion. As a result, there are substantial inherent limitations which must provide caution. The heterogeneity of the studied population provides multiple potential confounders such as differences in causes of death, underlying comorbidities, and duration of hemorrhage. Additionally, patients who died prior to obtaining a HgB value during the 24 hour window were excluded. A survivor bias likely exists, therefore, as those patients who died of exsanguination before this time may have benefited from aggressive blood product resuscitation. Furthermore, the determination of anatomic hemostasis was based on blood product administration rather than a surgical assessment of coagulation control. The reason for this was due to the limited ability to discern anatomic hemostasis from review of the medical records; prospective trials warrant a surgical, rather than resuscitation based, definition.⁷ In order to ensure sufficient power, trauma and non-trauma surgical patients were considered together. The aggressive resuscitation of trauma patients has been well delineated in the literature but not within non-trauma, non-cardiac surgery patients; whether the same premises of damage control resuscitation apply to other hemorrhaging populations is unclear. In fact, differing patient populations may require alternative resuscitation strategies and differing HTTs. Lastly, the odds of mortality were not adjusted for additional patient factors such as injury severity for trauma patients as well as sex, comorbidities, and vital signs. Importantly, the increased odds of death in the OT and UT cohorts was not necessarily due to excessive or insufficient administration of pRBCs; while there was a strong correlation with increased odds of mortality, causation is not implied. Further study in a prospective fashion accounting for potential confounders and mechanisms for the increased odds of death noted are necessary.

We believe that targeting an ideal HgB range after equilibration following anatomic hemostasis shows strong promise for the reduction of UT and OT events. This method may provide a mortality benefit to exsanguinating patients. While patient physiology remains critical to guide transfusion practice both during and after the MT event, additional tools must be developed to effectively monitor patients in order to ensure optimization of blood product transfusions. Prospective studies are mandatory to validate these tools' predictive ability as well as further refine the ideal HgB transfusion range during MT events. Until verification or modification of the HTT has been completed through these trials, however, we cannot recommend that it should be utilized clinically.

Acknowledgments

MICHAEL J. JOYNER, MD – GRANT MENTOR

THIS PUBLICATION WAS MADE POSSIBLE BY CTSA GRANT NUMBER UL1 TR000135 FROM THE NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES (NCATS), A COMPONENT OF THE NATIONAL INSTITUTES OF HEALTH (NIH). ITS CONTENTS ARE SOLELY THE RESPONSIBILITY OF THE AUTHORS AND DO NOT NECESSARILY REPRESENT THE OFFICIAL VIEW OF NIH.

References

1. Malone DL, Dunne J, Tracy JK, Putnam AT, Scalea TM, Napolitano LM. Blood transfusion, independent of shock severity, is associated with worse outcome in trauma. *J Trauma*. 2003 May; 54(5):898–905. discussion 905–7. [PubMed: 12777902]

2. Claridge JA, Sawyer RG, Schulman AM, McLemore EC, Young JS. Blood transfusions correlate with infections in trauma patients in a dose-dependent manner. *Am Surg.* 2002 Jul; 68(7):566–572. [PubMed: 12132734]
3. Teixeira PG, Onel D, Demetriades D, Inaba K, Shulman I, Green D, Plurad D, Rhee P. Blood transfusions in trauma: six-year analysis of the transfusion practices at a Level I trauma center. *Am Surg.* 2008 Oct; 74(10):953–957. [PubMed: 18942621]
4. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirement in critical care. *NEJM.* 1999; 340(6):409–417. [PubMed: 9971864]
5. Salpeter SR, Buckley JS, Chatterjee S. Impact of more restrictive blood transfusion strategies on clinical outcomes: a meta-analysis and systematic review. *Am J Med.* 2014 Feb; 127(2):124.e3–131.e3. Epub 2013 Oct 7. [PubMed: 24331453]
6. West MA, Shapiro MB, Nathens AB, et al. Inflammation and the Host Response to Injury Collaborative Research Program. Inflammation and the host response to injury, a large-scale collaborative project: Patient-oriented research core-standard operating procedures for clinical care. IV. Guidelines for transfusion in the trauma patient. *J Trauma.* 2006 Aug; 61(2):436–439. [PubMed: 16917462]
7. Holcomb JB, Tilley BC, Baraniuk S2, Fox EE, Wade CE, Podbielski JM, del Junco DJ, Brasel KJ, Bulger EM, Callcut RA, Cohen MJ, Cotton BA, Fabian TC, Inaba K, Kerby JD, Muskat P, O'Keeffe T, Rizoli S, Robinson BR, Scalea TM, Schreiber MA, Stein DM, Weinberg JA, Callum JL, Hess JR, Matijevic N, Miller CN, Pittet JF, Hoyt DB, Pearson GD, Leroux B, van Belle G. PROPPR Study Group. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA.* 2015 Feb 3; 313(5): 471–482. [PubMed: 25647203]
8. Johansson PI, Stensballe J, Oliveri R, Wade CE, Ostrowski SR, Holcomb JB. Blood. How I treat patients with massive hemorrhage. 2014 Nov 13; 124(20):3052–3058. Epub 2014 Oct 7.
9. Toy P, Bacchetti P, Grimes B, Gajic O, Murphy EL, Winters JL, Gropper MA, Hubmayr RD, Matthay MA, Wilson G, Koenigsberg M, Lee DC, Hirschler NV, Lowell CA, Schuller RM, Gandhi MJ, Norris PJ, Mair DC, Sanchez Rosen R, Looney MR. Recipient clinical risk factors predominate in possible transfusion-related acute lung injury. *Transfusion.* 2015 May; 55(5):947–952. [PubMed: 25488517]
10. So-Osman C, Nelissen R, Te Slaa R, Coene L, Brand R, Brand A. A randomized comparison of transfusion triggers in elective orthopaedic surgery using leucocyte-depleted red blood cells. *Vox Sang.* 2010 Jan; 98(1):56–64. Epub 2009 Jul 23. [PubMed: 19656349]
11. McIntyre L1, Hebert PC, Wells G, Fergusson D, Marshall J, Yetisir E, Blajchman MJ. Canadian Critical Care Trials Group. Is a restrictive transfusion strategy safe for resuscitated and critically ill trauma patients? *J Trauma.* 2004 Sep; 57(3):563–568. discussion 568. [PubMed: 15454803]
12. Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, Graupera I, Poca M, Alvarez-Urturi C, Gordillo J, Guarner-Argente C, Santaló M, Muñoz E, Guarner C. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med.* 2013 Jan 3; 368(1):11–21. [PubMed: 23281973]
13. Bush RL, Pevec WC, Holcroft JW. A prospective, randomized trial limiting perioperative red blood cell transfusions in vascular patients. *Am Journal of Surgery.* 1997; 174(2):143–148.
14. So-Osman C, Nelissen R, Te Slaa R, Coene L, Brand R, Brand A. A randomized comparison of transfusion triggers in elective orthopaedic surgery using leucocyte-depleted red blood cells. *Vox Sang.* 2010 Jan; 98(1):56–64. Epub 2009 Jul 23. [PubMed: 19656349]
15. Carson JL, Terrin ML, Noveck H, Sanders DW, Chaitman BR, Rhoads GG, Nemo G, Dragert K, Beaupre L, Hildebrand K, Macaulay W, Lewis C, Cook DR, Dobbin G, Zakriya KJ, Apple FS, Horney RA, Magaziner J. FOCUS Investigators. Liberal or restrictive transfusion in high-risk patients after hip surgery. *N Engl J Med.* 2011 Dec 29; 365(26):2453–2462. [PubMed: 22168590]
16. Brandstrup B, Svendsen C, Engquist A. Hemorrhage and operation cause a contraction of the extracellular space needing replacement—evidence and implications? A systematic review. *Surgery.* 2006; 139:419–432. [PubMed: 16546507]
17. Morrison CA, Carrick MM, Norman MA, Scott BG, Welsh FJ, Tsai P, Liscum KR, Wall MJ Jr, Mattox KL. Hypotensive resuscitation strategy reduces transfusion requirements and severe

- postoperative coagulopathy in trauma patients with hemorrhagic shock: preliminary results of a randomized controlled trial. *J Trauma*. 2011 Mar; 70(3):652–663. [PubMed: 21610356]
18. Joseph B, Pandit V, Aziz H, Kulvatunyou N, Zangbar B, Tang A, O' Keeffe T, Jehangir Q, Snyder K, Rhee P. Transforming hemoglobin measurement in trauma patients: noninvasive spot check hemoglobin. *J Am Coll Surg*. 2015 Jan; 220(1):93–98. Epub 2014 Oct 13. [PubMed: 25456784]
19. Moore LJ, Wade CE, Vincent L, Podbielski J, Camp E, Junco DD, Radhakrishnan H, McCarthy J, Gill B, Holcomb JB. Evaluation of noninvasive hemoglobin measurements in trauma patients. *Am J Surg*. 2013 Dec; 206(6):1041–1047. Epub 2013 Oct 21. [PubMed: 24157223]

KEY POINTS

Ideal pRBC transfusion practice in hemorrhage; Hemoglobin transfusion target and pRBC over-transfusion prevention

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

FIGURE 1.

The odds of death (Y-axis) based on the hemoglobin (HgB) value 24 ± 6 hours after anatomic hemostasis (X-axis). The odds of death are controlled for age, sex, and Charlson Comorbidity score. The inflection points for increased mortality odds were above 12.0 g/dL (pRBC over-transfusion) and below 8.0 g/dL (under-transfusion). The ideal HgB range was defined as 8.0 – 12.0 g/dL.

Figure 2.
Odds of packed red blood cell over-transfusion in massive transfusion patients based on age.

Figure 3.
Odds of packed red blood cell over-transfusion in massive transfusion patients based on the lowest systolic blood pressure recorded.

Table 1

Demographics and clinical course.

Feature	pRBC UT (n=38)	HTT (n=351)	pRBC OT (n=29)	UT vs HTT vs OT p-value	OT vs HTT p-value
Mean age	55.4 (14.1)	57.9 (16.7)	49.8 (22.8)	.039	.015
Male sex	21 (55%)	231 (66%)	20 (69%)	.389	.841
CCS	5.0 (3.0)	4.9 (3.2)	2.9 (2.7)	.005	.002
Lowest SBP during MT	59 (15)	61 (18)	74 (42)	.003	.001
Greatest HR during MT	105 (30)	114 (28)	129 (23)	.002	.004
Lowest pH during MT	7.15 (0.13)	7.23 (0.12)	7.19 (0.12)	<.001	.105

HTT = Hemoglobin Transfusion Target; CCS = Charlson Comorbidity Score; SBP = systolic blood pressure; MT = massive transfusion; HR = heart rate, UT = under-transfusion; OT = over-transfusion. Continuous variables are presented as means (standard deviation) and categorical percentages are presented as n (%).

Table 2

Cohorts of patients based on their categorization of hemoglobin values 24±6 hours after anatomic hemostasis.

Feature		Cohort	Odds of Death	Unadjusted Mortality
Hgb Cohort	<8.0 g/dL	pRBC under-transfusion	OR 3.5 (95% CI 1.7–7.3)	36.8%
	8.0–11.9 g/dL	reference	1.0	15.1%
	12.0 g/dL	pRBC over-transfusion	OR 2.7 (95% CI 1.2–6.5)	31.0%
Age	Per 10 years		OR 1.2 (95% CI 1.02–1.5)	
Sex	male		OR 0.81 (95% CI 0.48–1.3)	
CCS	Per 1 point		OR 0.95 (95% CI 0.86–1.05)	

pRBC = packed Red Blood Cell; CCS = Charlson Comorbidity Score; OR = Odds Ratio; CI = Confidence Interval

Table 3

Multivariable features associated with packed red blood cell over-transfusion.

Independent Variables	Odds Ratio (95% CI)	P-value	AUROC
Age, per 1 year <40	1.06 (1.03–1.13)	.003	0.733
Lowest SBP per mm Hg <50	1.06 (1.01–1.11)	.010	
Lowest SBP per mm Hg >70	1.09 (1.04–1.14)	<.001	

SBP = systolic blood pressure; Hg = mercury; CI = confidence interval, AUROC = area under the receiver operating curve.