

Transfusion Threshold Trials: The Need to Establish a Clear Difference in Transfusion Practice between Study Groups

To the Editor:

Thresholds for erythrocyte transfusion are currently under much scrutiny, with increasing evidence to support more restrictive transfusion practice,¹⁻⁵ and we read with interest the study by Pinheiro de Almeida *et al.*⁶ There is little dispute that patients with cancer who are anemic have poorer outcomes than those who are not anemic,⁷ but prospective data to support benefit from transfusion are lacking. Increasing concerns regarding risks such as transfusion-associated circulatory overload, transfusion-related acute lung injury, and alloimmunization have led to a number of randomized control trials addressing transfusion thresholds in well-defined patient groups such as patients treated in the intensive care unit (ICU): Transfusion Requirements in Critical Care (TRICC),¹ following hip (Functional Outcomes in Cardiovascular patients Undergoing Surgical hip fracture repair [FOCUS])³ and cardiac surgery (Transfusion Requirements After Cardiac Surgery [TRACS]),² and patients with acute upper gastrointestinal bleeding⁴ and sepsis (Transfusion Requirements In Septic Shock [TRISS]).⁵

There are no previous prospective randomized data examining transfusion thresholds in oncology patients; in their article entitled "Transfusion requirements in surgical oncology patients" published in the January edition of *ANESTHESIOLOGY*, Pinheiro de Almeida *et al.*⁶ randomize 198 critically ill patients following surgery for abdominal malignancy to restrictive (threshold 7 g/dl) and liberal (threshold 9 g/dl) strategies. They demonstrate an impressive and unexpected almost two-fold increase in their composite 30-day outcome (all-cause mortality, cardiovascular complications, acute respiratory distress syndrome, acute kidney injury requiring renal replacement therapy, septic shock, or reoperation) in the restrictive group. The outcome was reached in 35.6% in the restrictive group versus 19.6% in the liberal group ($P = 0.012$).

Thirty-day mortality was 8.2% (liberal) versus 22.8% (restrictive) ($P = 0.005$); this difference persisted at 60 days. The most common causes of death were septic shock and multisystem organ failure. Cardiovascular events and intraabdominal sepsis were more frequent in the restrictive group.

We question whether the differences observed are related to differences in transfusion practice or other confounding variables. A considerable 57.7% of those even in the liberal group were not transfused during their ICU stay, that is, were not subject to the intervention of interest. Although the authors state that differences in hemoglobin were statistically significant, this only relates to the hemoglobin pretransfusion and therefore does not include the 57.7% (liberal group) and 79.2% (restrictive group) that were not transfused. Although the target thresholds were 7.0 and

9.0 g/dl, patients were transfused on average at 6.8 and 7.9 g/dl, respectively, and all 13 protocol deviations in the liberal group occurred when patients with a hemoglobin less than 9.0 g/dl were not transfused (compared to all 7 deviations in the restrictive group occurring when transfusions were given to patients with hemoglobin greater than 7.0 g/dl). Patients in the liberal group received a median of 2 units during their ICU admission compared with 1 unit in the restrictive group ($P = 0.17$). There is a lack of clear separation in the hemoglobin levels between the two groups compared with previous large multicenter transfusion threshold trials.^{3,5}

The median duration for which patients remained in their randomized group (*i.e.*, the length of ICU stay) was only 4 days compared with 11 days in the TRICC trial and until discharge or death in the Villanueva and FOCUS trials. In this study, the small difference in hemoglobin concentration between the groups only emerges at 4 days. Furthermore, it is difficult to attribute such differences in outcomes to whether patients did or did not receive an average of one extra unit of blood. Taking all of these factors together, we feel it is doubtful whether the differences in outcomes can be attributed to differences in transfusion alone.

The results of this study are in stark contrast to other transfusion threshold studies that have supported the safety of restrictive strategies in patients with septic shock, upper gastrointestinal bleeding, following hip and cardiac surgery and during ICU admission, and even in those with cardiovascular comorbidities. The authors postulate that inclusion of both elective and emergency surgical patients may explain some of the differences between this and other trials, but the pivotal TRICC study similarly included elective and emergency admissions to the ICU,¹ and Villanueva *et al.*⁴ and Holst *et al.*⁵ report emergency admissions. Leukocyte-reduced blood, as used in this study, may negate some of the risks of transfusion associated with liberal strategies identified in the TRICC and TRACS studies but not in the more recent Villanueva *et al.*⁴ and TRISS studies that used leukocyte-reduced components. The FOCUS, TRISS, and Villanueva studies included patients with cancer although no subgroup analysis on these patients is currently available.

The authors go on to suggest that cancer patients may be more susceptible to impaired tissue oxygenation and that impaired microvascular flow below a hemoglobin concentration of 8.0 g/dl may be associated with postoperative complications in abdominal surgery. They also refer to a Korean propensity-matched study suggesting that transfused patients with septic shock have better outcomes⁸; this was not corroborated by the recent randomized controlled TRISS trial.

We note a small excess in major operations such as esophagectomy and gastroduodenopancreatectomy, as compared to cystectomy and hysterectomy, in the restrictive group. This may explain the excess of abdominal sepsis in this group as well as their excess mortality and increase in the composite 30-day outcome. There was also a small (albeit

nonsignificant) excess of patients with diabetes, chronic obstructive pulmonary disease, and congestive heart failure in the restrictive group. Adequate blinding is challenging for this patient group, and treating physicians were not blinded to the randomization. It is therefore possible that the rest of the care delivered was different between the groups. These confounding factors may have contributed toward the worse outcomes in the patients in the restrictive transfusion group.

The implications of this study could be substantial, and although the numbers of patients are small compared with other similar studies, the outcomes are apparently significant. However, the evidence that true differences in hemoglobin between the two groups was achieved is lacking, and furthermore, less than half of the patients even in the liberal group required transfusion and less than a third of patients in the study received any blood. This makes it difficult to assign differences in outcomes between the groups to transfusion.

Given the unexpected findings of this study, we would advise caution in interpreting the results. We feel differences in outcome cannot be attributed to the transfusion strategy alone. Further randomized studies are needed prior to alterations in clinical practice.

Competing Interests

The authors declare no competing interests.

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References

- Hébert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E: A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999; 340:409–17
- Hajjar LA, Vincent JL, Galas FR, Nakamura RE, Silva CM, Santos MH, Fukushima J, Kalil Filho R, Sierra DB, Lopes NH, Mauad T, Roquim AC, Sundin MR, Leão WC, Almeida JP, Pomerantzeff PM, Dallan LO, Jatene FB, Stolf NA, Auler JO Jr: Transfusion requirements after cardiac surgery: The TRACS randomized controlled trial. *JAMA* 2010; 304:1559–67
- 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; 365:2453–62
- 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; 368:11–21
- Holst LB, Haase N, Wetterslev J, Wernerman J, Guttormsen AB, Karlsson S, Johansson PI, Aneman A, Vang ML, Winding R, Neblich L, Nibro HL, Rasmussen BS, Lauridsen JR, Nielsen JS, Oldner A, Pettilä V, Cronhjort MB, Andersen LH, Pedersen UG, Reiter N, Wiis J, White JO, Russell L, Thornberg KJ, Hjortrup PB, Müller RG, Möller MH, Steensen M, Tjäder I, Kilsand K, Odeberg-Wernerman S, Sjøbø B, Bundgaard H, Thyø MA, Lodahl D, Mærkedahl R, Albeck C, Illum D, Kruse M, Winkel P, Perner A; TRISS Trial Group; Scandinavian Critical Care Trials Group: Lower *versus* higher hemoglobin threshold for transfusion in septic shock. *N Engl J Med* 2014; 371:1381–91
- Pinheiro de Almeida J, Vincent JL, Barbosa Gomes Galas FR, Pinto Marinho de Almeida E, Fukushima JT, Osawa EA, Bergamin F, Lee Park C, Nakamura RE, Fonseca SM, Cutait G, Inacio Alves J, Bazan M, Vieira S, Vieira Sandrini AC, Palomba H, Ribeiro U Jr, Crippa A, Dalloglio M, Del Pilar Estevez Diz M, Kalil Filho R, Costa Auler JO Jr, Rhodes A, Hajjar LA: Transfusion requirements in surgical oncology patients: A prospective, randomized controlled trial. *ANESTHESIOLOGY* 2015; 122:29–38
- Caro JJ, Salas M, Ward A, Goss G: Anemia as an independent prognostic factor for survival in patients with cancer: A systemic, quantitative review. *Cancer* 2001; 91:2214–21
- Park DW, Chun BC, Kwon SS, Yoon YK, Choi WS, Sohn JW, Peck KR, Kim YS, Choi YH, Choi JY, Kim SI, Eom JS, Kim HY, Cheong HJ, Song YG, Choi HJ, Kim JM, Kim MJ: Red blood cell transfusions are associated with lower mortality in patients with severe sepsis and septic shock: A propensity-matched analysis. *Crit Care Med* 2012; 40:3140–5

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Liberal Transfusion Practice or Perioperative Treatment of Anemia to Avoid Transfusion?

To the Editor:

With great interest we read the article by Pinheiro de Almeida *et al.*¹ on “Transfusion Requirements in Surgical Oncology Patients” that addresses a clinical problem of utmost importance and ongoing debate. However, there remain some concerns with the interpretation of data and conclusions that can be drawn from these results.

- Patients were included in this study if their hemoglobin level was more than or equal to 9 g/dl before admission to the intensive care unit (ICU). A hemoglobin level of 9 to 10 g/dl represents a state of severe anemia that occurred in a certain number of patients despite transfusion before randomization (fig. 3). Unfortunately, the incidence and severity of anemia according to the World Health Organization definition in the study groups is not reported. Regarding the further comorbidity profile of patients included, the number of patients with emergency operations ($n = 13$ *vs.* 9), congestive heart failure ($n = 6$ *vs.* 3), chronic obstructive pulmonary disease ($n = 9$ *vs.* 5), diabetes mellitus ($n = 26$ *vs.* 20), metastatic cancer disease ($n = 39$ *vs.* 32), and cerebrovascular disease ($n = 8$ *vs.* 2) were, at least numerically, higher in the restrictive group. It would be interesting whether the composite of these comorbidities was equally distributed between groups to better understand the interaction of anemia and preoperative