Editorial

The sicker the patient, the more likely that transfusion will be beneficial

Jean-Louis Vincent[1], Christophe Lelubre[2]

[1]Department of Intensive Care, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium; [2]Laboratoire de Médecine Expérimentale (ULB 222 Unit), Université Libre de Bruxelles, CHU de Charleroi, A. Vésale Hospital, Montigny-Le-Tilleul, Belgium

Correspondence to: Jean-Louis Vincent, MD, PhD. Department of Intensive Care, Erasme Hospital, Université libre de Bruxelles, Route de Lennik 808, Brussels 1070, Belgium. Email: jlvincent@intensive.org.

Provenance: This is an invited Editorial commissioned by Section Editor Dr. Xue-Zhong Xing [National Cancer Center (NCC)/Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC), Beijing, China].

Comment on: Bergamin FS, Almeida JP, Landoni G, *et al*. Liberal versus restrictive transfusion strategy in critically ill oncologic patients: The Transfusion Requirements in Critically Ill Oncologic Patients randomized controlled trial. Crit Care Med 2017;45:766-73.

Submitted Nov 01, 2017. Accepted for publication Nov 16, 2017.
doi: 10.21037/jtd.2017.11.102
View this article at: http://dx.doi.org/10.21037/jtd.2017.11.102

Although there is a general consensus that decisions to transfuse should not be based on hemoglobin concentrations alone (1), many people still limit blood transfusions to patients with hemoglobin concentrations less than 7 g/dL, because this strategy is easily included in a simple protocol (2). There are two conditions in which transfusions could be more liberal: one is in the presence of coronary artery disease and the other one is related to the severity of the critical illness.

Patients with acute coronary syndromes have usually been excluded from randomized controlled trials (RCTs) in this field (3). The reason for this decision is obvious: the primary response to normovolemic anemia is an adrenergic response that can increase myocardial oxygen demand. Blood transfusion has similar effects to those of beta-blocking agents but without reducing oxygen delivery to the tissues (4). It is quite surprising that a RCT was conducted on use of blood transfusions in patients with symptomatic coronary artery disease (5): the trial was rapidly discontinued when it was found that the mortality rate was substantially higher in the restrictive than in the liberal transfusion group (13% *vs.* 2%, respectively, P=0.03).

Critically ill patients may benefit from blood transfusions more than less severely ill individuals. This is not surprising. Relatively healthy individuals who have recently undergone surgery or trauma are able to recover slowly without particular support, even with relatively low hemoglobin concentrations. However, patients with or at risk of organ function have less physiological reserve and are more likely to be vulnerable to a decrease in hemoglobin concentration.

This latter point is illustrated well by a recent study by Bergamin *et al.* (6). The authors randomized 300 adult patients with cancer and septic shock at ICU admission to a liberal (n=149) or a restrictive transfusion strategy (n=151), using the now usual thresholds of 9 *vs.* 7 g/dL, respectively. Patients in the liberal group received a median of 1 [0–3] red blood cell (RBC) unit and the restrictive group a median of 0 [0–2] units. The patients were very ill, with a mean Simplified Acute Physiology Score (SAPS) II of about 57, a sequential organ failure assessment (SOFA) score of around 7 and an overall mortality rate close to 50%. The 28-day mortality rate in the liberal group was 45% (67 patients) *vs.* 56% (84 patients) in the restrictive group. At 90 days after randomization, the mortality rate was lower in the liberal than in the restrictive group (59% *vs.* 70%, P=0.03).

These investigators have considerable experience in this field and we have had the privilege to collaborate with them on several occasions (7,8). Unfortunately, the title of their paper did not accurately reflect the context of their study, referring to 'critically ill oncologic patients' but omitting to mention that the patients had septic shock, a much more important piece of information. Indeed, it is not clear why cancer would be a feature of importance in this acute setting. Transfusions have been reported to be associated

with greater occurrence of cancer recurrence in some studies (9), in relation to the immunomodulating effects of transfusions, but this effect, if present, would anyway not be relevant in such a short-term study.

We are surprised by the authors' conclusion that their results are not compatible with other trials in the field. On the contrary, we believe the results are as expected, because the sicker the patient, the greater the likely benefit of transfusion. One could argue that the results diverge somewhat from those of the Scandinavian study by Holst *et al.* (10), in which patients with septic shock randomized to two different transfusion strategies had similar outcomes. However, that study was rather a study of over-transfusion, as almost all patients in the liberal transfusion group received a blood transfusion, versus still almost two thirds of patients in the restrictive strategy group, a higher rate than in standard practice. At the other extreme, studies with only mildly ill patients have typically reported no differences in outcomes associated with a more liberal or a more restrictive transfusion strategy. Studies in patients with gastrointestinal bleeding (11) or in low- to medium-risk surgical patients (12) are examples of studies in which mortality rates were anyway quite low in both groups and could not be influenced by a different blood transfusion strategy. Even in the landmark study by Hebert *et al.* in ICU patients (3), where many patients were excluded before randomization, the overall mortality was less than 25%.

After all, with all their exclusion criteria, RCTs may not be the ideal method to obtain answers to questions related to optimal transfusion triggers. When evaluating any prospective RCT comparing different blood transfusion strategies, it is important to identify the number of patients who were not randomized because the study physician felt unhappy following a specific transfusion threshold. In the study by Hebert *et al.* (3) mentioned earlier, 87% of patients considered for inclusion were not randomized and as a consequence, the study had to be stopped before the end as a result of the slow enrollment rate. By contrast, in large observational studies of critically ill patients no patients are excluded and informed consent may not even be needed when data are de-identified. Analyses of several such databases (13,14) have shown lower mortality rates with more liberal transfusion strategies. Recently, results from the Intensive Care Over Nations (ICON) database of more than 9,500 ICU patients, showed that the hazard ratio for mortality after transfusion decreased with increasing admission severity scores (Vincent JL, unpublished data).

Hence, the results of the study by Bergamin *et al.* (6) are very compatible with the current thinking that the sicker the patient, the more likely they are to benefit from blood transfusion. The authors should not feel disconcerted by their findings; their contribution provides a useful and appreciated addition to the literature in this field.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Vincent JL. Indications for blood transfusions: too complex to base on a single number? Ann Intern Med 2012;157:71-2.
2. Carson JL, Guyatt G, Heddle NM, et al. Clinical Practice Guidelines From the AABB: Red Blood Cell Transfusion Thresholds and Storage. JAMA 2016;316:2025-35.
3. Hebert PC, Wells G, Blajchman MA, et al. 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.
4. Vincent JL, Van der Linden P. Restrictive versus more liberal blood transfusions? The answer is in your heart. Minerva Anestesiol 2016;82:511-3.
5. Carson JL, Brooks MM, Abbott JD, et al. Liberal versus restrictive transfusion thresholds for patients with symptomatic coronary artery disease. Am Heart J 2013;165:964-71.
6. Bergamin FS, Almeida JP, Landoni G, et al. Liberal versus restrictive transfusion strategy in critically ill oncologic patients: The Transfusion Requirements in Critically Ill Oncologic Patients randomized controlled trial. Crit Care Med 2017;45:766-73.
7. de Almeida JP, Vincent JL, Galas FR, et al. Transfusion requirements in surgical oncology patients: a prospective, randomized controlled trial. Anesthesiology 2015;122:29-38.
8. Hajjar LA, Vincent JL, Galas FR, et al. Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. JAMA 2010;304:1559-67.
9. Acheson AG, Brookes MJ, Spahn DR. Effects of allogeneic red blood cell transfusions on clinical outcomes in patients

undergoing colorectal cancer surgery: a systematic review and meta-analysis. Ann Surg 2012;256:235-44.
10. Holst LB, Haase N, Wetterslev J, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. N Engl J Med 2014;371:1381-91.
11. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med 2013;368:11-21.
12. Carson JL, Terrin ML, Noveck H, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. N Engl J Med 2011;365:2453-62.
13. Sakr Y, Lobo S, Knuepfer S, et al. Anemia and blood transfusion in a surgical intensive care unit. Crit Care 2010;14:R92.
14. Park DW, Chun BC, Kwon SS, et al. 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.

Cite this article as: Vincent JL, Lelubre C. The sicker the patient, the more likely that transfusion will be beneficial. J Thorac Dis 2017;9(12):4912-4914. doi: 10.21037/jtd.2017.11.102