Liberal Transfusion Strategy in the Perioperative Period

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Evgeny Fominskiy, Carmine D. Votta, and Vladimir V. Lomivorotov

14.1 General Principles

A proper oxygen and nutrients' supply is physiologically essential. Similarly, a prompt removal of carbon dioxide and catabolites is as much important. For these reasons, it is fundamental to assure an efficient blood perfusion to all tissues at any time. This is possible thanks to three strictly associated components: (1) *the heart*, (2) *the vascular system* (*arterial and venous*), and (3) *the blood*. The impairment of even only one of them may seriously compromise tissues' perfusion and thus cause one or more organ failure.

Oxygen delivery (DO_2) is the amount of oxygen delivered, through the blood, from the lungs to all tissues each minute. It depends on the cardiac output (CO) and the arterial content of oxygen (CaO_2):

$$DO_2 = CO \times CaO_2$$

CaO_2 is the sum of oxygen bound to hemoglobin and oxygen dissolved into the plasma and is calculated as follows:

$$CaO_2 = \left(1.34 \times Hb \times SaO_2\right) + \left(0.003 \times PaO_2\right)$$

where *1.34* is the amount of oxygen bound by each gram of hemoglobin (mL/g), *Hb* is the concentration (g/L) of hemoglobin in the blood, *SaO2* is the percentage of

E. Fominskiy (✉) • V.V. Lomivorotov
Department of Anaesthesia and Intensive Care, Academician EN Meshalkin, Novosibirsk State Budget Research Institute of Circulation Pathology, Novosibirsk, Russia
e-mail: evfominskiy@gmail.com

C.D. Votta
Department of Anesthesia and Intensive Care, San Raffaele Hospital, Via Olgettina 60, 20132 Milan, Italy

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arterial oxygen saturation of the hemoglobin, *0.003* is the solubility coefficient of oxygen into the blood (mL/L/mmHg) at body temperature (37 °C), and *PaO2* is the arterial partial pressure of oxygen (mmHg). The most important factor determining the overall CaO_2 is the Hb concentration, rather than PaO_2 (considering a normal PaO_2 of 95 mmHg, $0.003 \times 95 = 0.28$ mL/L). This may explain why it is so important to assure adequate hemoglobin levels.

In the perioperative periods, suboptimal hemoglobin concentrations before surgery are quite frequent (e.g., due to chronic diseases; acute, subacute, or chronic bleeding; renal failure; cancer; etc.). Furthermore, expected or unexpected bleeding during surgery may cause severe anemia or even worsen the anemic preexisting status. For this reason blood transfusion is quite important in this setting.

Hemoglobin levels have always been the most important parameter to guide transfusions, usually fixing at 8 g/dL the threshold for transfusion [1, 2]. However, in recent years concerns are rising about "when to transfuse." In particular, more liberal transfusion strategies with higher hemoglobin level as a limit to decide when to transfuse are emerging.

In this chapter, we will discuss the scientific evidences available at the moment about a more restrictive versus liberal transfusion strategy in the perioperative period.

14.2 Main Evidence

A 2012 Cochrane review analyzed 19 randomized controlled trials (RCTs), enrolling 6,264 patients overall, that compared restrictive versus liberal transfusion strategies in different clinical settings (surgery, acute blood losses, and/or trauma and critical care units) [3]. Results showed a reduction of the transfusion rates in the restrictive group compared to liberal group (risk ratio (RR) 0.61, 95 % confidence interval (CI) 0.52–0.72; $p < 0.00001$; $I^2 = 93\,\%$). Such results were not confirmed in the vascular surgery sub-analysis (RR 0.91, 95 % CI 0.77–1.08; $p < 0.3$). Heterogeneity among trials for this outcome was statistically significant (Chi2 = 238.95, df = 16, $p < 0.00001$, $I^2 = 93\,\%$). Furthermore, hospital mortality was 23 % lower in the restrictive group (RR 0.77, 95 % CI 0.62–0.95; $p < 0.018$; $I^2 = 0\,\%$). Thirty-day mortality, hospital length of stay, and complications (cardiac events, myocardial infarction, pulmonary edema, cerebrovascular accidents/stroke, pneumonia, and infection) were not different in the two groups.

In 2015, an update of the Cochrane review and meta-analysis [4] of both single-center and multicenter RCTs (overall 9,813 patients of both surgical and medical settings) confirmed the reduction of the transfusion need with the restrictive strategy versus the liberal one (RR 0.54, 95 % CI 0.47–0.63; $p < 0.001$; $I^2 = 95\,\%$). Even in this case, no difference in terms of mortality, myocardial infarction, overall morbidity, and adverse events (cardiac complications, renal failure, thromboembolic stroke, transient ischemic attack, or hemorrhage) was observed between groups. Only a possible association between the restrictive strategy and a reduced rate of infections was noted (RR 0.73, 95 % CI 0.55–0.98; $p = 0.03$; $I^2 = 53\,\%$).

Recently, three RCTs performed in perioperative period demonstrated benefits from a liberal transfusion strategy [5–7]. Two of them were not included in the 2015 update of the Cochrane review.

De Almeida and colleagues [5] studied 198 patients undergoing major abdominal surgery for cancer and who required postoperative ICU stay for at least 24 h. Patients were randomly assigned to either the restrictive or the liberal transfusion strategy group. Patients received erythrocyte units each time the hemoglobin level decreased below 7 g/dL (restrictive group) or 9 g/dL (liberal group) during their ICU stay. The authors observed, in the liberal strategy group, a lower 30-day (8[8.2 %] vs. 23[22.8 %]; $p=0.005$) and 60-day (11[11.3 %] vs. 24[23.8 %]; $p=0.022$) mortality rate compared to the restrictive strategy group. Furthermore, a lower incidence of overall major cardiovascular events in the liberal group (5[5.2 %] vs. 14[13.9 %]; $p=0.038$) and a higher incidence of intra-abdominal infections in the restrictive group (15[14.9 %] vs. 5[5.2 %]; $p=0.024$) were observed.

The Transfusion Indication Threshold Reduction (TITRe2) trial (17 cardiac surgery centers in the United Kingdom) randomized 2003 patients undergoing nonemergency cardiac surgery to the restrictive-threshold group (hemoglobin level of 7.5 g/dL) or to the liberal-threshold group (hemoglobin level of 9 mg/dL). Results of this trial showed a higher mortality rate within 3 months in the restrictive group than in the liberal one (4.2 % vs. 2.6 %; hazard ratio 1.64; 95 % CI 1.00–2.67; $p=0.045$). No differences were found between the two groups with regard to the other outcomes (infections, ischemic events, ICU, high-dependency unit, and hospital length of stay) [6].

The Transfusion Requirements in Frail Elderly (TRIFE) trial, conducted by Gregersen and colleagues, is a single-center trial that enrolled 284 patients, aged ≥65 years, undergoing surgery for unilateral hip fracture, coming from nursing homes or from sheltered housing facilities. Patients in the restrictive strategy group received transfusions if their postoperative hemoglobin levels were lower than 9.7 g/dL, while patients in the liberal strategy group received transfusions if postoperative hemoglobin levels were lower than 11.3 g/dL. The authors found no difference for the primary outcome (recovery from physical disabilities at 10, 30, and 90 days after surgery) between the two groups. Concerning the secondary outcome (30-day and 90-day mortality), no difference was found between groups analyzing the data by the intention-to-treat, while a higher 30-day mortality was observed in the restrictive group using the per-protocol analysis (HR 2.4; 95 % CI 1.1–5.2; $p=0.03$). Subgroup analysis showed a higher 90-day mortality in the nursing home patients of the restrictive group with both the intention-to-treat (HR 2.0; 95 % CI 1.1–3.6; $p=0.01$) and the per-protocol (HR 1.9; 95 % CI 1.0–3.4; $p=0.04$) methods [7].

These three RCTs raised the possibility that a more restrictive transfusion strategy may be associated with a higher mortality. For this reason and since the abovementioned Cochrane reviews considered RCTs conducted in different contexts (e.g., surgery, ICUs, etc.) without distinguishing among them and considered both adults and children, Fominskiy et al. performed a new meta-analysis of RCTs [8]. The authors considered RCTs that enrolled only adults (age ≥18 years). Furthermore, they analyzed separately studies performed in perioperative settings (17 studies of which 9 in orthopedic surgery, 5 in cardiac surgery, 1 in vascular surgery, 1 in cancer surgery, and 1 in obstetrics) and studies performed in critically ill contexts (10 studies) for a total of 11,021 patients. Fourteen trials were multicenter; 18 trials included more than 100 patients and 2 studies more than 1,000 patients. Results of this meta-analysis showed that, in perioperative setting, mortality for all causes is reduced with the liberal transfusion strategy groups compared with the restrictive transfusion strategy groups (Odds Ratio 0.81, 95 % CI 0.66–1.00; $p = 0.05$; $I^2 = 25\,\%$). In the critically ill setting, there was no difference in all-cause mortality between liberal and restrictive groups (RR 1.10, 95 % CI 0.99–1.23; $p = 0.07$; $I^2 = 34\,\%$). No differences were also found in all-cause mortality between liberal and restrictive strategies when considering together the perioperative and the critically ill settings (Odds Ratio 0.96, 95 % CI 0.78–1.18; $p = 0.68$). This is a further step forward in understanding the importance of tailoring the best transfusion strategy on each clinical setting.

Finally, another meta-analysis investigated separately six RCTs that assessed the effect of liberal RBC transfusion strategy versus restrictive RBC transfusion strategy in patients undergoing cardiac surgery, 19 RCTs that assessed the same effect in patients undergoing noncardiac surgery, and 39 observational studies that assessed the effect of RBC transfusion versus no transfusion on outcomes in patients undergoing cardiac surgery [9]. Results of the RCT analysis showed no differences between liberal and restrictive strategies on mortality for both cardiac and noncardiac surgery. Conversely, the analysis of the observational studies showed that transfusion is associated with an increased mortality compared with no transfusion (OR 2.72, 95 % CI 2.11–3.49; $p < 0.0001$; $I^2 = 93\,\%$). These contrasting results may be ascribed to the different nature of randomized controlled trials and observational studies. The high interstudies heterogeneity ($I^2 = 93\,\%$) of the latter confirms the weakness of observational studies.

14.3 Therapeutic Use

Deciding univocally when to transfuse a patient is still a challenge and a matter of debate. To use a single parameter, such as blood hemoglobin level, to guide the administration of RBC in patients with anemia is not always the right way to go. A lot of factors such as age, gender, disease's features and its development and worsening speed, the presence of comorbidities, functional organ reserve, etc., influence the compensatory reactions of the organism to anemia.

Etiology and pathophysiology of anemia are not the same in surgical and critically ill patients. Acute blood loss and hemodilution are the main causes of anemia in the perioperative period. Moreover, in the perioperative period, O_2 and nutrient demand is higher and thus anemia less well tolerated. Conversely, etiology of anemia in critically ill patients is quite always multifactorial including advanced chronic diseases, phlebotomy and hemorrhagic losses, substrate deficiency for RBC production, inappropriate erythropoietin production/release from the kidneys, poor erythroid response to preexisting anemia, reduced RBC survival, increased RBC destruction, and hemodilution [10]. Furthermore, the organism compensatory mechanisms to anemia are different in surgical and in critically ill patients. In fact a rapid anemia development requires a more rapid response to overcome the acute DO_2 reduction, while a more progressive anemia onset let the organism to adopt a series of molecular, cellular, and tissue modifications that make anemia tolerable [11]. For these reasons, it is important to consider and distinguish the different context in which RBC transfusions are required.

Nowadays there is increasing evidence that liberal RBC transfusion strategy can reduce mortality in the perioperative period, probably because an earlier restoration of blood lost, especially during surgery, limits tissue suffering. This is quite important in people whose needs are higher than usual like the ones undergoing surgical interventions whose metabolism is augmented [12], and therefore an optimal tissue perfusion and O_2 delivery should be assured at the best level.

Anyway, RBC transfusions are not free of risks. Despite large progress in methods and quality of blood components preparation, potential complications, such as transfusion-related immunomodulation, acute lung injury, microcirculatory dysfunction, and infection transmission, still remain [13]. Nevertheless, the use of RBC can be considered safe in appropriate patients and with appropriate amount [8, 9, 14].

Conclusion

In the perioperative setting, blood transfusion is an essential tool to face ongoing anemia, most often due to blood losses, and thus to assure a satisfying tissue delivery of oxygen and nutrients. Today there is a growing interest of the scientific community towards a more liberal transfusion strategy in this kind of patients. In fact, it has been one of the topics discussed in the international consensus conference on nonsurgical interventions that might influence perioperative mortality [15, 16]. However, further large RCTs are needed to better establish the most appropriate blood management strategies in other clinical settings (e.g., trauma, brain injury, etc.) and in different subgroups of patients (e.g., patients with or without preexisting anemia of any etiology, undergoing urgent or nonurgent surgery, with and without renal failure, hematologic malignancies, etc). Finally, another direction of research could be the investigation of other physiological triggers to guide blood transfusion that may allow a more selective and individualized RBC use.

Summary Table

Clinical summary					
Drugs	Indications	Cautions	Side effects	Dosage	Notes
Liberal versus restrictive transfusion strategy	Patients undergoing any kind of surgery	Blood transfusion should be individualized taking into account patient's comorbidities, preexisting chronic anemia, etc.	Transfusion-related immunomodulation, acute lung injury, microcirculatory dysfunction, infection transmission	Depending on hemoglobin level, hemodynamic response, signs of tissue's suffering, preexisting anemia, or cardiac disease	Further studies are needed so that more accurate indications can be given

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