Restrictive transfusion triggers in major orthopaedic surgery: effective and safe?

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In major orthopaedic surgical procedures, peri-operative blood loss and blunted post-operative erythropoiesis, due to surgery-induced inflammation, may lead to post-operative anaemia in almost 90% of patients. Allogeneic blood transfusion is the most frequently used measure for treating acute intra- and post-operative anaemia, especially in patients with low pre-operative haemoglobin levels and/or undergoing non-elective surgery, as it may increase the patients' haemoglobin levels quickly and effectively, albeit also transitorily.

The rationale behind allogeneic blood transfusion is to restore oxygen delivery and provide a reserve should further bleeding occur. It is generally assumed that, in the event of tissue hypoxia, the benefits on survival conferred by the allogeneic transfusion in certain patients clearly outweigh the risks. This goal can only be achieved if dual indicators for blood transfusion (level of oxygen carriers and evidence of the oxygen tissue debt of anaemic origin) are used. However, in everyday clinical practice, reliable indicators of oxygen deficit of anaemic origin (mixed venous blood saturation, partial tissue oxygen pressure, etc.) are often not available[1] and, consequently, decisions on transfusion are usually made just on the basis of the patient's haemoglobin level and/or symptoms. Thus, many allogeneic blood transfusions are unnecessarily given to patients with only relatively low haemoglobin levels and in controlled clinical scenarios, just expecting that transfusion of red blood cells will increase oxygen transport, thus alleviating tissue hypoxia and improving outcome. This hypothesised benefit of allogeneic blood transfusion has not been unequivocally demonstrated[2]. Only recently has it been shown that allogeneic blood transfusion produces a variable increment in brain tissue oxygenation, as assessed by direct measurement of partial tissue oxygen pressure, in patients with neurological trauma and documented oxygen deficit[3].

As a result of improved screening for detecting transfusion-transmitted infections and better product conservation methods, allogeneic blood transfusion is considered a safe treatment option in developed countries, although most clinicians do not realise the high cost of this therapeutic resource. However, as a biological product, allogeneic blood transfusion will never be risk-free: (i) screening methods for the detection of new infectious threats will only be implemented once a significant proportion of the transfused population has already been infected; (ii) "clerical mistakes" and administration of "wrong blood" are still too frequent (1/15,000-1/20,000); and (iii) the risk of complications such as graft-versus-host disease, metabolic disorders, bacterial contamination, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), and transfusion-related immuno-modulation (TRIM) still persists[4]. Regarding TRIM, data from different observational studies involving over 20,000 orthopaedic surgical patients strongly suggest that allogeneic blood transfusion is associated with a dose-dependent increase in the risk of post-operative infection and mortality[5-9]. Similar data have been reported for patients undergoing cardiac surgery[10-12]. Thus, available data argue for caution, not complacency in prescribing allogeneic blood transfusions.

However, as highlighted by several studies, there is a large inter-centre variability in the percentage of patients who receive allogeneic blood transfusion when undergoing a particular orthopaedic surgical procedure. In the Austrian benchmark study, Gombotz *et al*.[13] found a considerable variability in both allogeneic blood transfusion rate (16-85% for primary total hip replacement [THR]; 12-87% for primary total knee replacement [TKR]), and blood loss volume (25-60% of total red blood cell mass for THR, 24-47% for TKR) which mainly reflects differences in surgical techniques and physicians' opinions, rather than in patients' characteristics. Similarly, the Orthopaedic Surgery Transfusion Haemoglobin European Overview (OSTHEO) study and the Italian benchmark study showed significant variability in transfusion triggers for TKR and THR patients[5,14]. This variability also affects other orthopaedic and non-orthopaedic surgical procedures. It is well known that up to 40-50% of all units of allogeneic blood are used in the surgical setting and up to 60% of all transfusions are given to patients older than 65 years old, an age group of patients who are generally excluded from altruistic blood donation[15]. As a consequence all the foregoing, the demand for allogeneic blood transfusion may exceed the supply in certain areas.

In order to reduce variability in transfusion practice, both in the proportions of patients receiving allogeneic blood transfusion and in the volume of

blood administered per transfused patient, scientific societies have developed evidence-based guidelines and recommendations on the indications of allogeneic blood transfusion[16-19]. The final objective of these guidelines is a more rational and "restrictive" use of allogeneic blood transfusion in patients for whom pharmacological options are not available or can not be implemented (e.g., acute severe anaemia). Accordingly, in making a transfusion decision in euvolaemic, non-bleeding patients: (i) the risk of anaemia and the risks and benefits of red cell transfusion should be carefully balanced for each individual patient; (ii) the so-called "liberal" transfusion protocols (pre-transfusion haemoglobin concentration >9-10 g/dL) should be generally avoided; (iii) should allogeneic blood transfusion deemed necessary, single unit transfusions are desirable; and (iv) patients should be reassessed between transfusions to determine the remaining transfusion needs.

In this regard, the Transfusion Requirements In Critical Care (TRICC) trial demonstrated that the introduction of a restrictive transfusion protocol (transfusion trigger of Hb <7 g/dL) reduced the rate of allogeneic blood transfusions by 33% and the allogeneic blood transfusion index by 3 units per patient compared to a liberal transfusion protocol (transfusion trigger of Hb <10 g/dL)[20]. There were no differences in mortality rates between groups, not even for the subgroup of patients with significant cardiac disease, but the restrictive protocol resulted in a lower mortality rate among patients who were younger (<55 years) or less critically ill (APACHE score <20)[20]. Following the TRICC trial, a number of studies have demonstrated that the implementation of a restrictive transfusion trigger reduced transfusion rates and did not increase morbidity or mortality rates or the length of hospital stay in patients undergoing orthopaedic surgery[21-24] (Table I).

The exception is the study by Foss *et al.*[23], in which an increased mortality rate was observed in the restrictive transfusion group, but the study was not powered to detect differences in this outcome variable. Nevertheless, Rosencher *et al.*[25] have suggested that "we must now move on towards tailoring allogeneic blood transfusion administration to suit individual needs by adapting to ward routines, to logistical problems of obtaining blood in a timely fashion and to the kinetics of bleeding for each procedure" and that "according to the kinetics of bleeding, the transfusion trigger should be different in the recovery room and in the ward".

In this issue of Blood Transfusion, So-Osman *et al.*[26] performed a *post-hoc* analysis of data extracted from a previous randomised study on transfusion triggers using pre-storage leucocyte-depleted red blood cells in elective orthopaedic surgery[27]. They compared red blood cell use, hospital stay, post-operative complications and patients' quality of life, after reassigning patients to a "patient's risk-tailored restrictive" or "liberal" transfusion group, without altering the initial randomisation. Compared to patients in the liberal group, those in the restrictive group received fewer transfusions and had fewer post-operative infections and respiratory complications, whereas hospital stay, cardiovascular complications, mortality rate and change in quality of life scores were not different in the two groups. The author concluded that a restrictive transfusion protocol was not associated with a worse outcome and could even be beneficial in some aspects. Thus, these findings add to the concept

Table I - Randomised controlled studies comparing restrictive versus liberal transfusion triggers in orthopaedic patients.

Authors (year)	Transfusion trigger	Patients (N)	ABT rate N (%)	ABT volume (U/pte)	Cardiovascular morbidity N (%)	Infection N (%)	Length of stay (days)	30-day mortality N (%)
Carson *et al.* (1998)	L: Hb <10 g/dL	42	41 (98)	2.0 ± 0.9	ND	0 (0.0)	6.3 ± 3.4	1 (2.4)
	R: signs of acute anaemia or Hb <8g/dL	42	19 (45)	1.8 ± 1.1	ND	1 (2.4) Pneumonia	6.4 ± 3.4	1 (2.4)
Grover *et al.* (2006)	L: Hb <10 g/dL	109	46 (43)	0 (0-10)	2 (1.8)	5 (4.6)	7.5 (6-8)	1 (0.9)
	R: Hb <8 g/dL	109	37 (34)	0 (0-5)	5 (4.6)	4 (3.7)	7.3 (7-8)	0 (0.0)
Foss *et al.* (2009)	L: Hb <10 g/dL	60	44 (73)	2 (1-2)	1 (1.7)	11 (18.3)	18 ± 15	0 (0)
	R: Hb <8 g/dL	60	22 (37)	1 (1-2)	6 (10.0)	6 (10.0)	16 ± 12	5 (8)
Carson *et al.* (2011)	L: Hb <10 g/dL	1,007	970 (96)	1.9	114 (11.3)	83 (8.2)	USA	52 (5.2)
	R: signs of acute anaemia or Hb <8g/dL	1,009	415 (41)	1.6	135 (13.4)	59 (5.8)	3.7 ± 3.4 4.0 ± 3.9 Canada 12.0 ± 9.3 12.7 ± 9.5	43 (4.3)
So-Osman *et al.* (2013)	L: standard practice	304	119 (39.1)	1.0 ± 1.6	27 (8.9)	31 (10.2)	10.2 ± 7.4	3 (1.0)
	R: new risk-tailored uniform protocol**	299	79 (26.4)	0.6 ± 1.4	30 (10.0)	16 (5.4)	9.6 ± 5.1	0 (0)

Legend
ABT: allogeneic blood transfusion; Hb: Haemoglobin; L: liberal transfusion protocol; R: restrictive transfusion protocol. *Mean ± standard deviation Median (inter-quartile range); **See So-Osman *et al.*[26] for details.

that restrictive transfusion triggers are safe and effective for most surgical or critically ill patients when appropriately implemented[28]. However, as there are no trials, the effects of restrictive transfusion triggers in high-risk groups need to be tested in further large clinical trials[28]. Meanwhile, for patients presenting with acute myocardial infarction, unstable angina or other organ dysfunction (heart failure, respiratory insufficiency, sepsis, etc.) it seems sensible to adopt a less restrictive transfusion protocol aimed at maintaining haemoglobin levels between 9 g/dL and 10 g/dL[28,29].

Therefore, although the use of patient-based restrictive transfusion criteria is not the only strategy to reduce both the frequency and volume of allogeneic blood transfusion and, consequently, allogeneic blood transfusion-related risks, it does seem to be safe and should be the cornerstone of any blood conservation programme for orthopaedic surgery[30,31].

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