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Abstract: Liberal versus restrictive red blood cell (RBC) transfusion triggers have been debated for years. This review illustrates the human body's physiologic response to acute anemia and summarizes the evidence from prospective randomized trials (RCTs) for restrictive use of RBC transfusions in high-risk patients. During progressive anemia, the human body maintains the oxygen delivery to the tissues by an increase in cardiac output and peripheral oxygen extraction. Seven RCTs with a total of 5,566 high-risk patients compared a restrictive hemoglobin (Hb) transfusion trigger (Hb < 70 or < 80 g/l) with a liberal Hb transfusion trigger (Hb < 90 or < 100 g/l). Unanimously these studies show non-inferiority, safety, and a significant reduction in RBC transfusions in the restrictive groups. In one RCT mortality was higher in the liberal Hb transfusion group, and in two additional RCTs mortality of subgroups or after risk adjustment was significantly higher in the liberal Hb transfusion trigger groups. Conclusion: Strong RCT evidence suggests the safety of restrictive transfusion triggers. As a consequence, an Hb transfusion trigger of <70 g/l is recommended for high risk patients.

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Evidence Base for Restrictive Transfusion Triggers in High-Risk Patients

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Keywords

Red blood cell transfusions · Blood transfusion · Transfusion trigger · Patient blood management

Summary

Liberal versus restrictive red blood cell (RBC) transfusion triggers have been debated for years. This review illustrates the human body's physiologic response to acute anemia and summarizes the evidence from prospective randomized trials (RCTs) for restrictive use of RBC transfusions in high-risk patients. During progressive anemia, the human body maintains the oxygen delivery to the tissues by an increase in cardiac output and peripheral oxygen extraction. Seven RCTs with a total of 5,566 high-risk patients compared a restrictive hemoglobin (Hb) transfusion trigger (Hb < 70 or < 80 g/l) with a liberal Hb transfusion trigger (Hb < 90 or < 100 g/l). Unanimously these studies show non-inferiority, safety, and a significant reduction in RBC transfusions in the restrictive groups. In one RCT mortality was higher in the liberal Hb transfusion group, and in two additional RCTs mortality of subgroups or after risk adjustment was significantly higher in the liberal Hb transfusion trigger groups. **Conclusion:** Strong RCT evidence suggests the safety of restrictive transfusion triggers. As a consequence, an Hb transfusion trigger of <70 g/l is recommended for high-risk patients.

Introduction

Red blood cell (RBC) transfusions are widely used worldwide in primary health care in less developed and newly industrialized countries as well as for high-performance procedures in health care of high-income countries. Improved survival due to RBC transfusions has been shown in specific situations such as in severe malaria-induced anemia in children with a hemoglobin (Hb) concentration of < 39 g/l or an Hb < 47 g/l with concomitant respiratory distress [1–3]. RBC transfusions also improve survival of elderly patients undergoing noncardiac surgery with a preoperative Hb < 80 g/l [4]. In addition, the European Trauma Treatment Guidelines recommend maintaining an Hb level of 70–90 g/l in severely injured patients by cell salvage, if possible, and RBC transfusions, if necessary [5].

However, RBC transfusions have also been shown to result in an increased mortality, length of hospital stay, organ dysfunction (lung, kidney, heart), infections, transfusion reactions, and huge costs [6, 7]. Therefore, a targeted use of RBC transfusion is mandatory, including evidence-based RBC transfusion triggers.

Defining the critical transfusion trigger in patients is not trivial. However, understanding the underlying physiological response and compensatory mechanisms during progressive anemia may be one approach to find the critical Hb level at which a RBC transfusion would be necessary to avoid organ dysfunction or whole organism damage [8]. Another approach is to analyze outcome studies assessing the impact of different Hb transfusion triggers on clinically relevant outcomes such as mortality, morbidity, and the need for advanced life support. In this review we limit our analysis for both approaches to adult patients.

Last but not least only focusing on Hb transfusion triggers is an insufficient approach to the problems of RBC transfusion, patient safety, and outcome. The more holistic approach to patient safety and outcome is the concept of patient blood management which aims at improving outcome by correcting the three main factors resulting in adverse patient outcome, i.e., preoperative anemia [9, 10], perioperative RBC loss [11, 12], and RBC transfusions [6, 13].

Physiology of Progressive Anemia

Oxygen delivery and off-loading to the tissues is vital for our organism to maintain energy production by oxidation of glucose to carbon dioxide and water. In the mitochondria stepwise metabolism of the glucose molecule leads to the production of adenosine triphosphate (ATP). ATP hydrolysis to adenosine diphosphate by ATPases is an ubiquitous process to sustain cellular enzyme energy requirements. In aerobic conditions, one glucose molecule is metabolized to 30 molecules of ATP, whereas in anaerobic or hypoxic circumstances the glucose degradation stops at the level of 3 carbon atoms with lactate as an end product, resulting in an overall gain of 2 molecules of ATP only.

Oxygen delivery (DO_2) is the product of cardiac output and arterial oxygen content (CaO_2). CaO_2 is the sum of Hb-bound oxygen ($Hb \times 1.34 \times SaO_2$) and plasma-dissolved oxygen ($PaO_2 \times F$; $F = 0.0031$ if PaO_2 is in mm Hg, $F = 0.0233$ if PaO_2 is in kPa), whereby under atmospheric conditions the Hb-bound part is far greater (approximately 98%) than the plasma-dissolved part [8].

Therefore, oxygen delivery depends critically on cardiac output, Hb concentration, and SaO_2 . Hence tissue hypoxia (insufficient oxygen delivery) can be due to ischemia (reduction in cardiac output or blood supply), hypoxia (decrease of SaO_2), toxins (blocking Hb oxygen binding), and anemia.

Blood loss and concomitant crystalloid or colloid infusion results in normovolemic hemodilution, i.e. normovolemia with a decreased Hb concentration. Physiologically, cardiac output increases to compensate the lower CaO_2 at low Hb concentrations in order to maintain oxygen delivery. The increase in cardiac output is primarily due to an increase in stroke volume and inotropy and only secondarily due to an increase in heart rate. O_2 extraction increases simultaneously favoring O_2 off-loading to the tissue. During extreme anemia and hemorrhagic shock, cardiac output is additionally redistributed to preserve blood and oxygen delivery to the vital organs (heart and brain) [14].

When hemoglobin concentration is lowered to a critical value $Hb(crit)$, O_2 off-loading to the tissue is no more sufficient to maintain O_2 consumption. The $Hb(crit)$ can be experimentally determined by measuring the start of the decline of whole body or organ oxygen uptake. As a consequence and without further treatment, animals die within 3 h after reaching the $Hb(crit)$ [15]. By increasing the inspired O_2 concentration, an exaggerated level of hemodilution with a lower $Hb(crit)$ can be reached [16].

Acute anemia tolerance differs among organs. In anesthetized pigs, cellular signs of hypoxia in the kidney and skeletal muscle developed at significantly higher Hb concentrations than in the heart, brain, and liver [17]. Last but not least, anesthetic measures such as deep neuromuscular blockade [18], application of norepinephrine to treat severe arterial hypotension [19], and induction of hypothermia [20] can increase anemia tolerance. From a physiologic point of view, anemia tolerance thus is quite remarkable. Interestingly, the human body responds very similarly, and its compensatory capacity is largely maintained even in patients with cardiovascular diseases and also in the elderly [8, 14].

Prospective Randomized Studies on the Effect of Restrictive versus Liberal Hemoglobin Transfusion Triggers

The first prospective randomized study compared the effect of an Hb transfusion trigger of <70 g/l with that of a transfusion trigger of <90 g/l in general intensive care unit (ICU) patients ($n = 838$) [21]. 30-day mortality was not significantly different between the groups, but there was a trend ($p = 0.10$) towards better survival in the restrictive group. In two prospectively defined subgroups, in patients younger than 55 years and in patients with APACHE II scores of ≤ 20 , however, survival was significantly better in the restrictive transfusion groups. In addition, hospital mortality was lower in the restrictive group (22.2 vs. 28.1%; $p = 0.05$), and there was significantly less multiple organ dysfunction in the restrictive versus the liberal RBC transfusion group [21].

In the next prospective randomized study, the effect of an Hb transfusion trigger of <80 g/l was compared with that of a transfusion trigger of <100 g/l in patients ($n = 502$) undergoing cardiac surgery [22]. Primary outcome, a composite of mortality and major morbidity (cardiogenic shock, acute respiratory distress syndrome, or acute renal injury requiring renal replacement), was similar in both groups. However, when analyzed independently of group assignment, each RBC transfusion significantly increased the risk of 30-day mortality or clinical complications by 20% (hazard ratio 1.2, 95% CI 1.1–1.4; $p = 0.002$).

Also in elderly high-risk patients ($n = 2,016$) with hip fracture and signs of coronary artery disease and a postoperative Hb < 100 g/l, the effect of a liberal Hb transfusion trigger of <100 g/l was compared with a restrictive transfusion trigger (combination of well-defined symptoms of anemia or an Hb < 80 g/l) in a prospective randomized study [23]. 60-day mortality was similar in the restrictive (6.6%) and the liberal group (7.6%), and also the inability to walk was similar between the groups. The authors subsequently analyzed long-term survival over a median of 3 years. There were 432 deaths in the liberal group and 409 deaths in the restrictive group (hazard ratio 1.09, 95% CI 0.95–1.25; $p = 0.21$). In only 1 of 18 subgroup analyses there was a trend ($p < 0.10$) towards a higher or lower mortality in patients randomized to the liberal Hb transfusion trigger. Interestingly, a trend towards a higher mortality was observed in patients with coronary artery disease randomized to the liberal Hb transfusion trigger (hazard ratio 1.26, 95% CI 1.04–1.54; $p = 0.06$). Causes of death did not differ between groups ($p = 0.99$) [24].

In patients ($n = 912$) with acute upper gastrointestinal bleeding, the effect of an Hb transfusion trigger of <70 g/l was compared with that of an Hb transfusion trigger of <90 g/l in a prospective randomized fashion [25]. 45-day survival was significantly better in the restrictive (95%) than in the liberal group (91%), with a hazard ratio for death of 0.55 (95% CI 0.33–0.92; $p = 0.02$) favoring the restrictive RBC transfusion regimen. In addition, the rate of re-bleeding was significantly lower in the restrictive than in the liberal group (10 vs. 16%; $p = 0.01$); moreover, less emergency surgery was required (2 vs. 6%; $p = 0.04$), complication rate was lower (40 vs.

Table 1. Prospective randomized studies on the effect of restrictive versus liberal hemoglobin transfusion triggers

	Study population	Leukoreduction	Storage duration (median), days	RBC transfusion before enrollment
Hébert et al. 1999 [21]	general ICU (n = 838)	no	unknown	2.5 U/patient (restrictive) 2.3 U/patient (liberal)
Hajjar et al. 2010 [22]	cardiac surgery (n = 502)	no	3	none
Carson et al. 2011 [23]	hip fracture (n = 2,016)	90%	22	1.8 U/transfused patient (restrictive) 1.8 U/transfused patient (liberal)
Villanueva et al. 2013 [25]	upper GI bleeding (n = 912)	100%	15	none
Walsh et al. 2013 [26]	mechanical ventilation (n = 100)	no	21	71% with a median of 3 U/patient (restrictive) 67% with a median of 2 U/patient (liberal)
Robertson et al. 2014 [27]	traumatic brain injury (n = 200)	100%	unknown	none
Holst et al. 2014 [28]	septic shock (n = 998)	100%	unknown	10% with a median of 2 U/transfused patient (restrictive) 12% with a median of 2 U/transfused patient (liberal)

ICU = Intensive care unit; U = unit; GI = gastrointestinal.

48%; $p = 0.02$) and length of hospital stay was shorter (9.6 vs. 11.5 days; $p = 0.01$) in the restrictive versus the liberal group.

In a feasibility study including 100 patients, Walsh et al. [26] studied the effect of a restrictive Hb transfusion trigger (Hb < 70 g/l) vs. a liberal Hb transfusion trigger (Hb < 90 g/l) in patients older than 55 years who were ventilated mechanically for at least 4 days in the ICU. The Hb level was significantly different between the groups during the study period of 14 days (Hb difference = 14 g/l, 95% CI 1.2–1.6 g/l; $p < 0.001$). Fewer patients (–22%) randomized to the restrictive group were transfused and received a median of 1 RBC transfusions less ($p = 0.002$). Ventilation-free days tended to be higher (38 days) in the restrictive group than in the liberal group (27 days), and also 180-day mortality tended to be lower in the restrictive group (37%) when compared to the liberal group (55%). While these differences did not reach statistical significance, this study clearly shows that a liberal transfusion regimen did not facilitate weaning nor influenced mortality favorably.

Recently the effect of erythropoietin (yes/no) and Hb transfusion trigger (Hb < 70 g/l vs. Hb < 100 g/l) was compared in a prospective randomized factorial design (2 × 2) study in patients (n = 200) with acute traumatic brain injury [27]. The primary outcome was favorable neurologic outcome as assessed by the Glasgow Outcome Score at 6 months. Multiple secondary outcomes were also assessed prospectively. The administration of erythropoietin did not affect any outcome, and there was also no interaction between erythropoietin administration and the Hb transfusion levels. Glasgow Outcome Score at 6 months was similar in both transfusion groups, but disability tended to be less (5 vs. 8; $p = 0.06$) in the restrictive vs. the liberal group, and there were fewer thrombotic complications in the restrictive vs. the liberal group (8 vs. 22%; $p = 0.009$).

Last but not least, the effect of a restrictive (Hb < 70 g/l) vs. a liberal (Hb < 90 g/l) transfusion regimen on outcome of patients (n = 998) with septic shock has been compared in a prospective randomized study [28]. The primary outcome was 90-day mortality; secondary outcome was the need for advanced support measures (vasopressors, inotropes, mechanical ventilation, and renal-replacement therapies) within the first 28 days. Mortality and the need for advanced support measures were similar between both groups.

Interestingly, in all studies mentioned in this section, the lack of efficacy and the side effect profile of liberal transfusion regimens do not appear to be related to the populations studied, irrespective of the facts whether leukoreduced or non-leukoreduced RBCs were transfused, how long the RBCs were stored before use (where this information is available), or whether RBCs had been transfused prior to study enrollment or not (table 1).

Meta-Analyses

There are two important meta-analyses that need to be presented here. In 2012 Carson et al. [29] analyzed 19 prospective randomized trials comparing restrictive and liberal transfusion regimens, including a total of 6,264 patients. This meta-analysis clearly showed that a restrictive transfusion regimen reduced the need for RBC transfusions by 39% (relative risk 0.61, 95% CI 0.52–0.73), hospital mortality by 23% (relative risk 0.77, 95% CI 0.62–0.95), and infections by 19% (relative risk 0.81, 95% CI 0.66–1.00). 30-day mortality (–15%) just missed statistical significance (relative risk 0.85, 95% CI 0.70–1.03). However, the last 2 big prospective randomized studies in patients with upper gastrointestinal bleed-

ing (n = 912) and with septic shock (n = 998) were not yet included, and since both had either a significant effect or a trend towards a better survival in the restrictive groups it may be expected that an updated meta-analysis including these two studies would show a long-term survival benefit for patients treated according to a restrictive transfusion regimen.

The second meta-analysis was performed in 2014 by Rohde et al. [30] including 18 prospective randomized studies with 7,593 patients. They found that a restrictive RBC transfusion regimen resulted in a reduction of postoperative infections by 12% (relative risk 0.88, 95% CI 0.78–0.99; p = 0.033) and of postoperative serious infections by 18% (relative risk 0.82, 95% CI 0.72–0.95; p = 0.006). Interestingly, when the meta-analysis was restricted to studies with only leukoreduced RBCs, the reduction of all types of infections decreased by 20% (relative risk 0.80, 95% CI 0.67–0.95; p = 0.001). This clearly shows that the infection risk due to RBC transfusion is neither eliminated nor reduced by leukoreduction.

Hemoglobin Transfusion Trigger

The combined evidence thus suggests that a liberal RBC transfusion regimen is not beneficial but potentially harmful for the patients. In high-risk patients, such as ICU patients, elderly patients with coronary artery disease, patients with upper gastrointestinal bleeding, patients with traumatic brain injury and patients with septic shock, an Hb transfusion trigger of <70 g/l is safe and helps avoiding transfusion-related complications. The <70 g/l Hb transfusion trigger thus is established as the 'new normal' in all critical patients [31] with the potential exception of patients with an acute coronary syndrome in which an Hb transfusion trigger of <80 g/l might be adequate [32].

Remarkably, Goodnough et al. [33] succeeded in implementing a restrictive transfusion regimen in their center by an intelligent blood ordering system. The percentage of RBC transfusions at an Hb > 80 g/l thereby decreased from approximately 60 to below 30%. In a subsequent study, Goodnough et al. [34] analyzed the effect of this change in transfusion policy on outcome and found a reduction of length of hospital stay from 10.1 to 6.2 days (p < 0.001) and of mortality from 5.5 to 3.3% (p < 0.001) in transfused patients.

Conclusion

Compensatory mechanisms such as the increase of cardiac output and oxygen extraction allow the human body to tolerate low Hb values well. This compensatory capacity is largely maintained in patients with cardiovascular diseases and also in the elderly. Pro-

spective randomized studies confirm this conclusion showing that liberal Hb transfusion regimens do not offer any outcome benefit to high-risk patients but in quite a number of situations inflict harm. Scientific evidence thus clearly mandates restrictive Hb transfusion triggers also for high-risk patients. Today the best investigated Hb transfusion trigger for high-risk patients is <70 g/l.

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None of the above listed companies and/or entities have been directly or indirectly involved in discussing and/or developing this manuscript or parts thereof. None of them have financially contributed to this endeavor in whatever form, neither directly or indirectly. Therefore, it is beyond my capacity to tell whether any of the above listed companies and/or entities do or do not have a direct financial interest in the subject matter or materials discussed in this manuscript.

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