Red blood cell transfusion in critically ill patients: from data to decision

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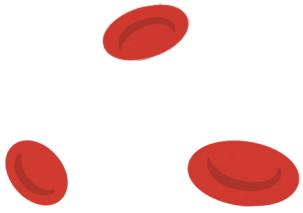
BLOOD IS NOT FOR EVERYONE: THE USEFULNESS OF RED CELL TRANSFUSION

STATE OF THE ART

Translation of original article: "Bloed, niet voor iedereen weggelegd."



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KEY POINTS

Increasing evidence for the limited effect and adverse effects of erythrocyte transfusion has led to a decrease in the number of red blood cell transfusions in the last 20 years.

The results of randomized controlled trials suggest that a hemoglobin level of 7 g/dL (4.4 mmol/L) as threshold for red cell transfusion does not affect clinical outcomes in most hemodynamically stable patients with acute anemia as compared to a higher transfusion threshold.

The effect of red blood cell transfusion in a patient with anemia does not only depend on his or her hemoglobin concentration, but also on other clinical factors that affect the balance between oxygen supply and oxygen consumption.

The Dutch '4-5-6' rule for the indication of red cell transfusion takes into account a number of important clinical factors, however, results of recent studies suggest that strict application of this rule will lead to unnecessary transfusion.

New research on this topic aims to quantify the effect of red cell transfusion in different relevant subgroups of patients

ABSTRACT

Increasing evidence on the limited effect and the adverse consequences of erythrocyte transfusion has led to a large drop in the number of blood transfusions over the last 20 years. The results of randomized studies suggest that in most hemodynamically stable patients with acute anemia a hemoglobin transfusion threshold of 7 g/dL (4.4 mmol/L) for blood transfusion has the same outcomes as a higher transfusion threshold. The effect of blood transfusion in patients with anemia not only depends on their hemoglobin level, but also on other clinical factors that play a role in the balance between oxygen supply and consumption. The Dutch '4-5-6' rule for indication for blood transfusion takes a number of important clinical factors into account, however, results of recent research suggest that the strict application of this rule will lead to unnecessary transfusions. New research in this area focusses on the quantification of the effect of blood transfusion in various combinations of relevant patient characteristics.

A 59-year-old woman has undergone surgical resection of a colorectal carcinoma. The day after the surgery she is admitted to the surgical unit. She has a history of myocardial infarction, type 2 diabetes and hypertension for which she has been taking medication. Preoperatively, the patient was in good condition and her hemoglobin concentration was 11.6 g/dL (7.2 mmol/L). The patient's postoperative recovery is uneventful except for an asymptomatic, normovolemic anemia with a hemoglobin concentration of 7.6 g/dL (4.7 mmol/L). There are no signs of active blood loss or cardiac ischemia. Would you transfuse this patient with red blood cells?

The life-saving properties of allogeneic erythrocyte transfusion, further referred to as blood transfusion, have been undisputed since the first experiments in patients with life-threatening bleeding.[1] After the discovery of the ABO blood groups in 1900 and the success of blood transfusions during World War I, transfusion became more and more widespread in medicine. Not only for major bleeding, but also for other indications such as normovolemic anemia.[2] Due to the widespread use, physicians were also increasingly confronted with side effects of blood transfusion, including infections, allo-immunization, and immunomodulation.

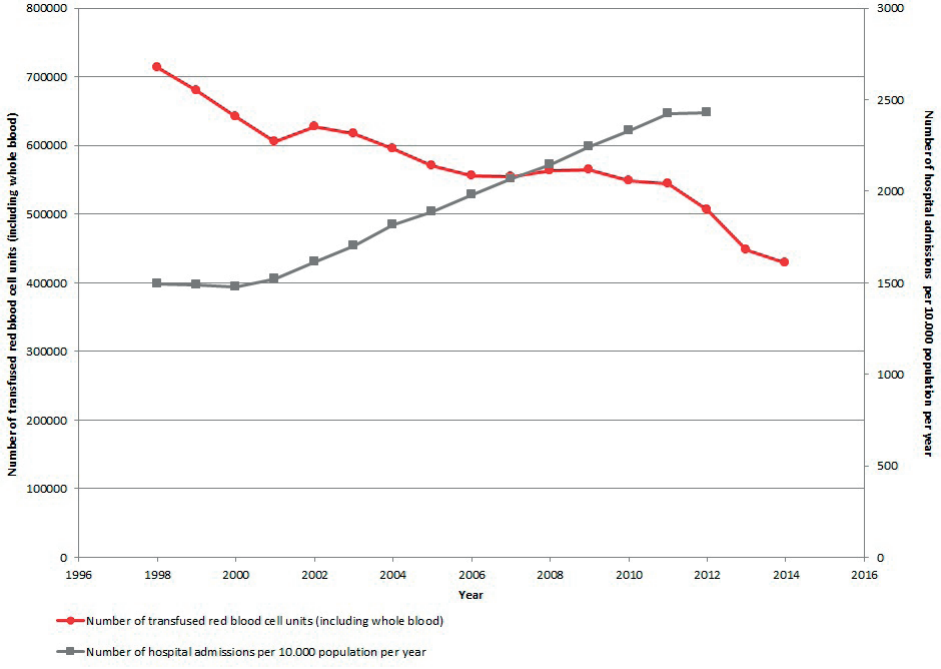

Figure Annual number of transfused red blood cell units in the Netherland, including whole blood (red line; data source: Sanquin Blood Banking). The annual number of hospital admission is shown for comparison (grey line: total hospital admission per 10 000 population per year; data source: CBS, Kerncijfers)

Increasing insight, both into the adverse effects and limited effects of blood transfusion on clinical outcomes, led to a steady decrease of hemoglobin thresholds for blood transfusion during the last 20 years. This is reflected in a significant decrease in blood consumption in hospitals in the Netherlands. The figure shows that the decline in blood consumption still continues.

In this article we discuss the currently available evidence on indications for blood transfusion in hemodynamically stable adults with acute anemia. Additionally, we discuss the question whether fresh blood is better than old blood.

SEARCH STRATEGY

We searched for relevant scientific literature in PubMed using a combination of the following search terms and their synonyms: 'red blood cell transfusion', 'mortality, and 'morbidity'. We only included studies published between 1st of January 1998 to 14th of September 2015. We excluded animal studies, articles written in languages other than English, case reports, case series and letters to the editor. The selection of articles was based on the level of evidence, methodological quality, publication date and clinical relevance. The full search strategy can be found in the supplemental material (Appendix 1).

INDICATION AND EFFECT OF BLOOD TRANSFUSION

Red cell transfusion to 'normalize' low hemoglobin concentrations

A hemoglobin threshold, the value of hemoglobin below which blood transfusion is indicated, was first reported in literature in 1942. Hemoglobin concentrations below this threshold were considered 'the enemy' that had to be fought. This threshold was set at hemoglobin levels of 10 mg/dL (6.3 mmol/L) or lower, or at a hematocrit of 30% or lower.[3] For many years, these thresholds, also known as the '10/30 rule' were used in daily clinical practice. To this day, the Hb concentration is still the most important parameter on which we base our transfusion decisions.

Complications

At the end of the 20th century, it turned out that HIV and hepatitis C virus can be transmitted through blood transfusions. Therefore, the complications of blood transfusion were examined more closely. Table 1 summarizes the transfusion-related complications. Discussion of these complications is beyond the scope of this article. Due to these

transfusion-related complications – including infectious complications – the risk/benefit balance of red blood cell transfusion became an important and critical focus of attention.

Table 1 Transfusion-related complications

Non-infectious complication	Infectious complications
Acute hemolytic transfusion reaction	Transfusion-transmitted bacterial infection
Delayed hemolytic transfusion reaction	Transfusion-transmitted viral infection (CMV, Parvo B19, hepatitis, HIV)
Anaphylactic transfusion reaction	Variant Creutzfeldt-Jakob disease
Mild allergic transfusion reaction	Others (e.g., parasitic infections)
(Febrile) non-hemolytic transfusion reaction	
Transfusion-related acute lung injury (TRALI)	
Transfusion-associated circulatory overload (TACO)	
Post-transfusion purpura (PTP)	
Transfusion-associated graft-versus-host disease	
Secondary hemochromatosis	
Immunomodulation	

‘Evidence’ for the efficacy of blood transfusion

The “Transfusion Requirements In Critical Care” (TRICC) study, a landmark trial, randomized patients admitted to the intensive care unit (ICU) to a ‘restrictive transfusion strategy’ (transfusion trigger of 7 g/dL) versus a ‘liberal transfusion strategy’ (transfusion trigger of 10 g/dL).[4] The study demonstrated no difference in 30-day mortality rate between both groups. Several other transfusion trigger trials followed after the publication of the TRICC trial, studying similar transfusion triggers in different patient categories. Table 2 presents the meta-analyses of the randomized controlled trials comparing the clinical effects of different transfusion strategies. The majority of these meta-analyses found no difference in clinical outcomes (mortality, infections and myocardial infarction) between a restrictive and liberal transfusion strategy. Only one meta-analysis of trials in ICU patients and patients with gastrointestinal bleeding reported lower mortality in the restrictive transfusion strategy group compared to the liberal strategy group.[5]

Table 2 Meta-analyses of transfusion trigger trials

Year of publication	Study population	Number of included RCTs (number of patients)*	Hb transfusion threshold (g/dL)		Relative risk or odds ratio (95% CI)†			
			Restrictive strategy	Liberal strategy	Mortality	Infection	Pulmonary edema	Myocardial infarctions
2012[6]	Heterogeneous‡	11 (*n*= 4979)	7.0 – 9.0	9.0 – 10.0	0.85 (0.70-1.03)	0.81 (0.66-1.00)	0.72 (0.31-1.70)	0.88 (0.38-2.04)
2014[5]	Critically ill (including pediatric patients) and upper gastrointestinal bleeding	3 (*n*= 2364)	7.0	9.0 – 10.0	0.81 (0.61-0.96)	0.86 (0.73-1.00)	0.48 (0.33-0.73)	0.44 (0.22-0.89)
2014[7]	Thoracic surgery	7 (*n*= 1272)	7.0 – 9.0	8.0 – 10.0	1.12 (0.65-1.95)	1.23 (0.85-1.78)	unknown	0.94 (0.30-2.99)
2015[8]	Heterogeneous§	9 (*n*= 5707)	7.0 – 9.0	9.0 – 13.0	0.86 (0.74-1.01)	0.73 (0.55-0.98)	unknown	1.28 (0.66-2.49)
2015[9]	Hip fracture surgery	5 (*n*= 2683)	8.0 – 9.7	9.0 – 11.3	1.09 (0.79-1.49)	0.74 (0.52-1.05)	unknown	1.69 (1.04-2.78)

* Pooled number of patients is presented. Outcome measure was mortality

† Relative risks and odds ratios for 4 clinical outcome measures are presented comparing restrictive versus liberal transfusion strategy

‡ Patients with upper gastro-intestinal bleeding, trauma, cardiosurgical patients, vascular surgery patients, orthopedic patients, critically ill patients (including pediatric patients) and cardiology patients

§ Patients with upper gastro-intestinal bleeding, trauma (including traumatic brain injury), cardiosurgical patients, vascular surgery patients, orthopedic patients, critically ill patients (including pediatric patients) and cardiology patients

Limitations of the research results

Results of the trigger trials do not allow to conclude that transfusion is only beneficial at hemoglobin concentrations below 7 g/dL (4.4 mmol/L). First, performance bias could have led to biased results. Due to the unblinded study design, there is a possibility that the care that is provided differed between the restrictive transfusion strategy and the liberal strategy. For example, patients in the restrictive-strategy group could have received more supportive treatments or additional red cell transfusions to improve oxygen delivery. As shown in Table 3, the relatively high percentage of protocol violations and so-called 'escape transfusions" suggest that performance bias might have occurred. Secondly, many older transfusion trigger trials enrolled a small fraction of the evaluated patients (see table 3). Clinicians were uncomfortable with the idea of assigning a high-risk patient to a restrictive-strategy group, or a low-risk patient to the liberal-strategy group. This raises questions about the generalizability of the results. Thirdly, strict adherence to a fixed-dose regimen is inconsistent with current clinical transfusion practice outside a trial. Red cell transfusion in critically ill patients is titrated based on other clinical parameters. The results of transfusion trigger trials only provide information regarding the difference in effect between the two transfusion strategies. A superior transfusion strategy could still be inferior to the current titrated transfusion practice.[10] At last, in several studies the mean hemoglobin concentration before transfusion was often higher than the hemoglobin threshold specified in the research protocol (see Table 3).[4] For example, the mean hemoglobin concentration in patients who received red cell transfusion in the restrictive-strategy group of the TRICC trial was 1.5 g/dL (almost 1 mmol/L) higher (8.5 g/dL) then transfusion trigger of 7 g/dL (4.4 mmol/L). Interestingly, international red cell transfusion guidelines only report on the restrictive hemoglobin trigger of 7 g/dL (4.4 mmol/L).

Table 3 Comparison of studies with respect to protocol violations, number of included patients different and hemoglobin thresholds [*]

Year of publication	Study population	Hb transfusion threshold (g/dL)	Transfused patients[†] (%)	Protocol violations (%)	Hb level before transfusion (g/dL); mean (SD)	Included patients (%)[‡]
1999[4]	Adult critically ill	7.0 vs. 10.0	67 vs. 100	1.4 vs. 4.3	8.5 (0.7) vs. 10.7 (0.7)[§]	41
2010[11]	Cardiothoracic surgery	8.0 vs. 10.0	47 vs. 78	1.6 vs 0.0	9.1 (0.8) vs. 10.5 (0.8) [§]	25
2011[12]	High-risk patients after hip surgery	8.0[‖] vs. 10.0	41 vs. 97	5.6 vs 9.0	7.9 (0.6) vs. 9.2 (0.5)	56
2013[13]	Acute gastrointestinal bleeding	7.0 vs. 9.0	49 vs. 86	9.0 vs 3.0	7.3 (1.4) vs. 8.0 (1.5)[¶]	96
2014[14]	Septic shock	7.0 vs. 9.0	64 vs. 99	5.9 vs 2.2	7.7 (7.7 – 7.7) vs. 9.4 (9.0- 9.4)[**]	96
2015[15]	Cardiothoracic surgery	7.5 vs. 9.0	53 vs. 92	9.7 vs 6.2	Not presented	Incalculable

[*] Only trials with more than 400 included patients are presented

[†] The percentage of transfused patients in the restrictive arm versus the percentage of transfused patients in the liberal arm is presented

[‡] The percentage of all eligible patients that are included

§ Mean daily hemoglobin level

[‖] Or symptoms of anemia

[¶] Nadir hemoglobin level during admission

[**] median (interquartile range) or daily nadir hemoglobin level during first 7 days of the admission

Observational research

In contrast to the randomized trigger trials, the comparison in observational studies is made between transfusion and no transfusion. We included an overview of the meta-analyses of observational studies in the supplementary material. All of the meta-analyses report worse clinical outcomes in transfused patients compared to non-transfused patients. Caution is needed in the causal interpretation of the reported associations, because confounding by indication and incorrect model specification could have biased these results. Reasons to transfuse a patient are also risk factors for a worse outcome. Often, no clear distinction is made between the effect of red cell transfusion and the effect of the indication for red cell transfusion.[16] In addition, most analyses do not address time-varying exposure or time-varying confounding.

WHEN TO TRANSFUSE?

Due to the limitations of clinical transfusion research, we still not exactly know when the intended effects of red cell transfusion outweigh the adverse effects. Results of randomized controlled trials have shown that patients with orthopaedic trauma, septic shock or upper gastrointestinal bleeding do not benefit from red cell transfusions at hemoglobin concentrations above 7 g/dL (4.4 mmol/L). [4,13,14,17] The use of a restrictive transfusion threshold will reduce the number of transfused patients and the number of units transfused, thereby reducing the risk of transfusion-related adverse reactions. The currently available evidence base is insufficient to support a restrictive transfusion strategy in other patient categories, including patients with myocardial infarction or neurotrauma.

Patient specific need for blood transfusion

At the individual level, the question remains whether a restrictive transfusion trigger is beneficial. Besides potentially harmful over-or undertreatment, the balance between over- and undertreatment differs per individual patient. Red blood cell transfusion is usually administered to improve oxygen delivery in order to prevent hypoxic tissue injury. Hypoxic tissue injury will occur when the oxygen delivery does not meet tissue oxygen demands. Besides anemia, which limits the oxygen transport capacity, other factors such as partial oxygen tension, hemoglobin oxygen affinity, structure and function of the microcirculation, oxygen extraction, metabolism of the patient, and the compensation mechanism to increase the cardiac output, influence the balance between oxygen delivery and oxygen demand. For example, patients with cardiovascular disease have a higher mortality risk compared with patients without cardiovascular disease with the same level of anemia.[18] This might be explained by the fact that patients with cardiovascular disease lack the ability to increase their cardiac output to compensate for the reduced oxygen delivery. Patients with high cardiac risks therefore may benefit from red cell transfusion

at higher hemoglobin levels. A pilot study in 110 patients with symptomatic coronary artery disease did report lower mortality in patients in whom the aim was to achieve a hemoglobin concentration of at least 10 g/dL (6.3 mmol/L).[17] Two other recent studies suggested restrictive transfusion strategy could lead to undertreatment. In a study among patients undergoing cardiac surgery, the mortality, one of the secondary outcome measures, was higher in the restrictive treatment arm (transfusion at hemoglobin level of Hb 7.5 g/dL (4.7 mmol/L)) as compared to patients in the liberal treatment arm (transfusion at hemoglobin level of 9 g/dL (5.6 mmol/L)).[15] Another randomized trial among surgical oncology patients also found a favourable effect of a liberal transfusion trigger. The liberal transfusion strategy with a transfusion trigger 9 g/dL (5.6 mmol/L) significantly reduced the risk of the primary outcome, a composite outcome of mortality and morbidity after 30 days, compared with the restrictive transfusion strategy with a hemoglobin trigger of 7 g/dL (4.4 mmol/L).[19]

More than restoration of low hemoglobin levels

The question remains how we can identify patients who will benefit from red blood cell transfusion. Benefit should be defined as improvement of clinical outcome instead of the restoration of the hemoglobin level. In the Netherland the so-called “4-5-6” rule is used for patient with acute normovolemic anemia. Depending on the presence of co-morbidity, the threshold for red cell transfusion varies between 4.0 mmol/L (6.4 g/dL) and 6.0 mmol/L (9.7 g/dL). Although the “4-5-6” rule offers some guidance in the transfusion decision, results of randomized trials show that strict application of this rule will result in overtreatment in some patients. These trials included critically ill patients, elderly patients with orthopedic trauma, patients with upper gastrointestinal bleeding, and patients with septic shock.[4,12-14] Just like the 4-5-6-rule, the more recent international guideline for critically ill patients also recommends to take into account other factors than the hemoglobin concentration in the decision to transfuse.[20] The recommended transfusion trigger is 7 g/dL (4.4 mmol/L), except for patients with acute coronary syndrome, severe sepsis, traumatic brain injury or subarachnoid hemorrhage. In these patient groups higher transfusion triggers (8-10 g/dL; 5-6.3 mmol/L) are recommended. Besides these specific groups of patients, the guidelines state that other co-morbidities or acute illness related factors can modify clinical decision-making. The authors of the guideline do not further specify these other factors. Ongoing research in the field of blood transfusion focuses on the identification and quantification of the role of these factors.

RED-CELL STORAGE DURATION

Old, but not out of date

Fresh blood is better. This is a deeply rooted belief among many. During refrigerated storage, the red cells undergo several changes (table 4).[21] These changes raise questions about the risks of 'old' blood. Numerous studies that compared outcomes among patients receiving blood of longer versus shorter storage durations suggest that fresh blood is better. However, the results of these observational studies should be interpreted with caution due to methodological flaws.[22] More recent randomized trials and observational studies with higher methodological quality did not find a difference between old and fresh blood with respect to clinical outcome.[23-25] The "Age of Blood Evaluation"(ABLE) study is a multicenter randomized controlled clinical trial among 2510 critically ill patients, comparing red cells stored for less than 8 days with standard-issue red cells (mean storage time: 22 days). Transfusion of fresh red cells did not decrease the 90-day mortality. The same was observed for the secondary outcome measures, and also in the subgroup analyses.[23]In the same period, the results of the 'Red Cell Storage Duration Study' (RECESS) were published. The authors report no differences with respect to the effect of 'fresh' erythrocytes (<10 days old) as compared to 'old' erythrocytes (>20 days). Shorter storage durations do not confer any benefits for patients undergoing cardiac surgery.[25] Interestingly, results of an observational study do even suggest that old blood might be better than fresh blood.[24] Based on these results, the 'first-in, first out' policy of blood banks together with a maximal storage duration of 35 days seems appropriate.

Table 4 Red cell changes during storage

Metabolic changes	Physical changes
Lower pH	Changes of red cell membrane
Reduced ATP levels	Deformation of red cells
Reduced 2,3-biphosphoglycerate levels	Others
Increased potassium levels	
Others	

CONCLUSION

Results of randomized controlled trials comparing different transfusion triggers support the notion that a red cell transfusion at hemoglobin concentration above 7.0 g/dL (4.4 mmol/L) does not improve clinical outcomes. To what extent these results can be explained by so-called 'escape transfusion' and other interventions is unclear. However, it is clear that these results do not apply to all hemodynamically stable adult patients with

acute anemia. Based on theoretical grounds, a restrictive transfusion strategy might be harmful for patients with acute coronary artery disease, severe sepsis, traumatic brain injury or subarachnoid hemorrhage. The decision to transfuse should therefore not be based only on the Hb concentration and/or admission diagnosis. Other clinical factors such as age, metabolic demands and cardiopulmonary reserve should be considered in the transfusion decision. Although this last statement lacks any supporting evidence, it is widely used in the literature and transfusion guidelines.

Take home messages

- Red cell transfusions are usually administered in order to improve oxygen delivery – prevent hypoxic tissue injury - in case of anemia.
- Over the past 20 years hemoglobin triggers for transfusion in patients with normovolemic anemia has become increasingly restrictive
- The decision to transfuse red cells is mainly based on hemoglobin levels
- A hemoglobin trigger of 7 g/dL (4.4 mmol/L) is safe in most hemodynamically stable patients with acute anemia.
- Other co-morbidities or acute illness related factors can modify clinical decision-making with respect to blood transfusion in individual patients.
- Storage durations shorter than 4 weeks seem not to confer any benefits for patients.

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SUPPLEMENTAL MATERIAL

Available at https://www.ntvg.nl/uploads/2021/a9/40/8_/a9408_supplement.pdf [Dutch]

PubMed search strategy

Figure 2 Flow chart illustrating the search strategy for studies of the effect of red cell transfusion on clinical outcomes (mortality, morbidity)

Table Overview of systematic reviews and meta-analyses of observation studies