HEMATOLOGY, TRANSFUSION AND CELL THERAPY

www.rbhh.org

Special article

Guidelines on transfusion of red blood cells: Prognosis of patients who decline blood transfusions

Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular Project guidelines: Associação Médica Brasileira – 2018

Dante Mário Langhi Junior[a], *Dimas Tadeu Covas*[b], *Jose Francisco Comenalli Marques*[c,*], *Alfredo Mendrone Junior*[d], *Eugênia Maria Amorim Ubiali*[b], *Gil Cunha De Santis*[b], *Gizela Kelmann*[e], *Wanderley Marques Bernardo*[e]

[a] *Faculdade de Ciências Médicas da Santa Casa de São Paulo (FCMSCSP), São Paulo, SP, Brazil*
[b] *Hemocentro de Ribeirão Preto, Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo (HCFMRP-USP), Ribeirão Preto, SP, Brazil*
[c] *Hemocentro da Universidade Estadual de Campinas (Unicamp), Campinas, SP, Brazil*
[d] *Fundação Pró-Sangue, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP), São Paulo, SP, Brazil*
[e] *Associação Médica Brasileira (AMB), São Paulo, SP, Brazil*

ARTICLE INFO

Article history:
Received 2 August 2018
Accepted 6 August 2018
Available online 25 September 2018

Introduction

The guidelines project is a joint initiative of the *Associação Médica Brasileira* and the *Conselho Federal de Medicina*. It aims to bring together information in the scientific literature to standardize conduct in order to help decision-making during treatment. The data contained in the following articles were prepared by and are recommended by the *Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular* (ABHH). Even so, all possible medical approaches should be evaluated by the physician responsible for treatment depending on the patient's characteristics and clinical status.

* *Corresponding author at:* Universidade Estadual de Campinas, Faculdade de Ciências Médicas da UNICAMP, Banco de Sangue, Rua Carlos Chagas 480, Barão Geraldo CEP, 13086-878 Campinas, SP, Brazil.
E-mail address: marquesj@unicamp.br (J.F. Marques).
https://doi.org/10.1016/j.htct.2018.08.001

Description of the method used to gather evidence

These guidelines are the result of a systematic review centered on the Evidence-Based Medicine movement, where clinical experience is integrated with the ability to critically analyze and rationally apply scientific information, thereby improving the quality of medical care.

Questions are structured using the Patient/Problem, Intervention, Comparison and Outcome (PICO) system, allowing the identification of keywords which were the basis of evidence-based search strategies in the major scientific databases [Medline (via PubMed), EMBASE, Central (Cochrane), Lilacs (via BVS) and CINAHL via EBSCO] and manual searches.

Degree of recommendation and level of evidence

A: Major experimental and observational studies
B: Minor experimental and observational studies
C: Case reports (non-controlled studies)
D: Opinion without critical evaluation based on consensus, physiological studies or animal models

Objective

This article presents the guidelines prognosis of patients who decline blood transfusions.

PICO system

Using the PICO system, the P corresponds to patients who refused blood transfusions, I to the indication of transfusions (blood or red blood cells), and O to the outcomes (death, morbidity, survival, quality of life).

Thus, 14 studies were found and selected to answer the clinical question (Appendix A).

What clinical-laboratory parameters indicate the need to transfuse red blood cells?

Introduction

The purpose of these guidelines is to answer the question as to whether there are parameters, timing, clinical signs or situations that indicate that the refusal of a red blood cell transfusion can lead to death or sequelae. The scientific basis for formulating a satisfactory answer to the question at hand can be drawn from three types of study:

(1) Experimental studies in animals and humans in which isovolemic anemia was induced by dilution in order to evaluate its effects.
(2) Observational studies of patients (in general, Jehovah's Witnesses – JW) who have declined red blood cell transfusions, especially in the context of surgery.
(3) Studies that evaluated the use of restrictive [hemoglobin (Hb) concentration of 7–8 g/dL] and liberal (Hb of 9–10 g/dL) transfusion triggers for various clinical conditions with randomization of participants.

Experimental studies

Animal studies have shown the physiological changes that occur when isovolemic anemia is brought about by controlled dilution. For example, a study in mice showed that deaths only started when the Hb concentration fell below 5.0 g/dL; 100% of the animals had died when Hb was below 2.0 g/dL.[1] Similar results were observed in other animals, such as pigs and baboons.[2] In healthy humans subjected to isovolemic anemia due to dilution, no signs of tissue hypoxia were observed at an Hb concentration of 5.0 g/dL.[3] It is important to stress that animals and humans undergoing induced anemia were all healthy and were kept at rest. Thus, one cannot extrapolate any conclusions obtained under clinically controlled conditions to other situations, for example, in patients with surgical trauma, who often have additional physiological demands that are possibly more difficult to achieve with an Hb concentration of only 5.0 g/dL.

Patient refusal

There are situations in which red blood cell transfusions are not possible, for example, when the patient refuses, whether for religious reasons (JW) or for another personal reason. Some observational studies in the USA have shown the consequences of postoperative anemia. The two most important showed that the morbidity and mortality rates for the Hb range of 7.0–8.0 g/dL are very low, but these increase progressively by 2.0- to 2.5-fold for each 1 g/dL reduction of Hb. The mortality rate reaches 100% of individuals with Hb less than or equal to 2.0 g/dL.[4,5]

Several randomized trials have evaluated restrictive and liberal transfusion triggers and have contributed to establishing lower levels of Hb that still seem to be safe in specific clinical conditions. Recent reviews have shown that the adoption of transfusion triggers of low Hb levels (7–8 g/dL – restrictive indication) did not result in more unfavorable outcomes than those seen with higher triggers (Hb 9–10 g/dL – liberal transfusion).[6,7]

Specific situations, such as cardiac surgery, in which there is great transfusion demand with 25–95% of patients requiring transfusions, represent a great challenge. In this context, cardiac surgery in patients who refuse transfusion require extensive collaboration between the surgeon, the anesthetist, and the clinical staff.[8]

A meta-analysis with six retrospective studies compared the immediate outcomes of JW patients and controls submitted to cardiac surgery (coronary artery bypass grafting, heart valve surgery and ascending aortic surgery) performed both electively and as urgencies/emergencies. JW patients presented higher Hb levels in the postoperative period (11.5 g/dL vs. 9.8 g/dL; p-value < 0.001) and significantly lower blood loss compared to controls (402 mL vs. 826 mL; p-value < 0.001). JW and controls had similar post-operative outcomes. However, JW presented a trend, albeit without statistical significance, of

lower rates of early mortality, reoperations for bleeding, atrial fibrillation, stroke, myocardial infarction and length of intensive care unit stay, with limited heterogeneity between the studies. No studies reported transfusion-related reactions in the control group, but it has been shown that additional interventions in patient blood management are effective and may improve the immediate outcome. Meticulous surgical technique and hemostasis are the key to prevent intraoperative and postoperative blood loss.[9]

Strategies aimed at reducing the need for transfusion in cardiac surgery can be adopted after careful discussion and decisions with individual patients.[9] These include:

(1) Preoperative preparation

- Optimization of Hb concentration: erythropoietic stimulating agents, iron, folic acid, vitamin B12.
- Optimization of hemostasis: application of hemostasis tests (e.g. thromboelastometry), suspension of anticoagulants and antiplatelet agents, administration of vitamin K.

(2) Intraoperative

- Intraoperative blood recovery.
- Minimizing blood loss: meticulous surgical technique, off-pump surgery, topical hemostatic agents, minimally invasive cardiopulmonary bypass, retrograde priming, normothermia or mild hypothermia, antifibrinolytics, use of protamine sulfate to reverse heparin action, and coagulation management depending on the severity of the bleeding and the result of the thromboelastometry.

(3) Postoperative

- Postoperative blood recovery.
- Minimizing blood loss.
- Optimization of hemostasis and the adoption of more conservative criteria to indicate reoperation due to bleeding.
- Optimization of Hb concentration: erythropoietic stimulating agents, iron, folic acid and vitamin B12.

The sample size of the most important randomized study about red blood cell transfusion in cardiac surgery was 2430 patients in each group. Just over half ($n = 1271$; 52.3%) of the patients in the restrictive-transfusion strategy group (Hb < 7.5 g/dL) received transfusions, while 72.6% ($n = 1765$) of the participants in the liberal-transfusion strategy group (Hb < 9.5 g/dL) were transfused (Odds ratio: 0.41; 95% confidence interval: 0.37–0.47). Mortality was 3.0% in the restrictive group and 3.6% in the liberal group (Odds ratio: 0.85; 95% confidence interval: 0.62–1.16). Other clinical outcomes (myocardial infarction, left ventricular function, renal function) did not differ between the groups either.[10]

A retrospective study involving patients submitted to cardiac surgery showed only a trend of longer hospitalization (1.3 days) in the intensive care unit for JW patients compared to the control group (p-value = 0.08). There was no statistical difference in the rate of early postoperative mortality or postoperative in-hospital morbidity between the two groups.[8]

Patients with intraoperative Hb levels below 8 g/dL or with a drop of Hb ≥50% were investigated in a prospective cohort of 23,860 consecutive patients (JW = 270) who underwent cardiac surgery over a 15-year period. JW and non-JW patients who had received one unit of packed red blood cells in the intraoperative period were compared. Moreover, patients who had received one unit of packed red blood cells in the intraoperative period were compared with matched non-transfused patients. The postoperative outcomes analyzed were acute myocardial infarction, dialysis, stroke and death. Postoperative complications increased with decreasing intraoperative Hb levels in both JW and non-JW patients. There was no significant difference in the incidence of postoperative complications between these two groups (Odds ratio: 1.44; 95% confidence interval: 0.63–3.29) as well as between patients who received intraoperative red blood cell transfusions and non-transfused patients (Odds ratio: 0.94; 95% confidence interval: 0.72–1.23). The data showed that intraoperative anemia is associated with adverse outcomes in the postoperative period of cardiac surgery, and the transfusion of one packed red blood cell unit did not influence this outcome.[11]

In a retrospective cohort study, risk factors related to mortality in JW patients (≥15 years of age) with anemia (Hb ≤ 8 g/dL) were evaluated and a mortality risk score was created (Hamilton anemia mortality risk score). One hundred and eight JW patients enrolled in the study received folic acid, iron, erythropoietin and cyanocobalamin and 70% underwent surgeries. The mean Hb concentration was 6.3 ± 1.25 g/dL. Scores of 1, 2 or 3 were assigned to each risk factor for mortality identified by the study according to the statistical significance of each variable: Shock (3), acute gastrointestinal bleeding (2), pneumonia (2), intra-hospital Hb (1), sepsis (1), worsening of congestive heart failure (1) and neurological complications (1). Considering the absolute risk of mortality, patients with a cumulative score of 0–2 had a 4% risk, a score of 3–4 was correlated to a 29% risk, those with a score of 5 had a 40% risk and a score of ≥6 was correlated to a 67% risk of mortality.[12]

In a retrospective study, the results of emergency non-transfusion laparotomies of 20 JW women in a state of hemorrhagic shock due to uterine rupture were compared with 45 women submitted to surgical procedures for similar indications who received transfusions. The intraoperative blood loss ranged from 500 to 1500 mL in both groups, 88% of the non-transfused patients survived with the deaths being attributed to peritonitis; 84.4% of transfused patients survived, six died due to peritonitis and one death was caused by disseminated intravascular coagulation. The need for ventilatory support was similar in both groups. The duration of postoperative hospital stay in patients who received and those who did not receive transfusions was 8 and 7 days, respectively.[13]

A study by Carson et al. evaluated 300 over 18-year-old patients who presented Hb ≤ 8 g/dL in the postoperative period and declined red blood cell transfusions due to religious reasons (JW). Patients were stratified by postoperative Hb and evaluated for mortality and morbidity (myocardial infarction, cardiac arrhythmia, congestive heart failure and infection) within 30 days after surgery. No death was reported in the group of patients who presented Hb between 7.1 and 8.0 g/dL in the postoperative period and only 9.4% had a morbid event. In the group of patients with Hb between 4.1 and 5.0 g/dL, mor-

tality was 34.4% and 57.7% presented some morbid event. After adjusting for age and heart disease, the risk of morbidity and mortality increased by 2.5-fold for each 1 g/dL reduction of Hb.[4]

In a study with a design similar to that of Carson,[4] Shander et al. evaluated 293 patients with postoperative Hb levels ≤8.0 g/dL who declined transfusions. The risk of death (unadjusted) increased by 2.04 times for every 1 g/dL reduction in Hb. The risk of death after adjusting for other significant factors (urgency, classification of the American Association of Anesthesiology and age) was 1.82 for every 1 g/dL drop in Hb.[5]

A small, randomized study ($n = 109$) suggested that patients with acute coronary disease and/or stable angina who received restrictive transfusions (Hb < 8.0 g/dL) presented higher mortality than those who received liberal transfusions (Hb < 10.0 g/dL) (Odds ratio: 2.38; 95% confidence interval: 0.99–5.73). However, patients in the restrictive group were, on average, seven years older than those in the liberal group; this may have had some negative impact on this group. Therefore, this result must be interpreted with some caution.[14]

Recommendations

Considering the studies analyzed and the considerations set out above, some guidelines can be suggested:

- Anemia with Hb levels up to 7–8 g/dL in clinically stable patients can be safely managed without transfusion or with little transfusion.
- The adoption of restrictive transfusion triggers (Hb ≤ 7–8 g/dL) seems to be justified for most clinical situations, except perhaps in patients with acute coronary disease with or without stable angina.
- For lower postoperative Hb levels (≤8 g/dL), morbidity and mortality increase progressively with the drop in Hb (approximately two-fold for each 1 g/dL drop in Hb).

Conflicts of interest

The authors declare no conflicts of interest.

Appendix A.

1. Clinical question

What clinical-laboratory parameters indicate the need to transfuse red blood cells?

2. Structured question (PICO)

Patient: Jehovah's Witnesses; Treatment refusal
Intervention: Blood transfusion; red blood cell transfusion
Comparison: None
Outcome: death, morbidity, survival, quality of life

3. Initial eligibility criteria for studies

- Components of PICO
- No time limit
- Languages: English, Portuguese and Spanish
- Observational comparative studies (cohort and/or before and after)
- Comparative experimental studies (clinical trial)

4. Search strategies

- (((blood Transfusion* OR erythrocyte Transfusion* OR red blood cell Transfusion*))) • AND ((Jehovah's Witnesses) OR Treatment Refusal)
- Manual search - References, revisions and guidelines

5. Selection of articles

Initially selected by the title, sequentially by the abstract, and finally by the full text, the latter being subjected to critical evaluation and extraction of outcomes.

6. Critical evaluation and strength of evidence

The strength of the evidence of the studies was defined taking into account the study design and the corresponding risks of bias, the results of the analysis (magnitude and precision), relevance and applicability (Oxford/GRADE).[15–18]

REFERENCES

1. Tsui AK, Marsden PA, Mazer CD, Adamson SL, Henkelman RM, Ho JJ, et al. Priming of hypoxia-inducible factor by neuronal nitric oxide synthase is essential for adaptive responses to severe anemia. Proc Natl Acad Sci U S A. 2011;108(42):17544–9.
2. Klein HG, Spahn DR, Carson JL. Red blood cell transfusion in clinical practice. Lancet. 2007;370(9585):415–26.
3. Weiskopf RB, Viele MK, Feiner J, Kelley S, Lieberman J, Noorani M, et al. Human cardiovascular and metabolic response to acute, severe isovolemic anemia. JAMA. 1998;279(3):217–21.
4. Carson JL, Noveck H, Berlin JA, Gould SA. Mortality and morbidity in patients with very low postoperative Hb levels who decline blood transfusion. Transfusion. 2002;42(7):812–8.
5. Shander A, Javidroozi M, Naqvi S, Aregbeyen O, Caylan M, Demir S, et al. An update on mortality and morbidity in patients with very low postoperative hemoglobin levels who decline blood transfusion (CME). Transfusion. 2014;54 10 Pt 2:2688–95, quiz 2687.
6. Carson JL, Guyatt G, Heddle NM, Grossman BJ, Cohn CS, Fung MK, et al. Clinical practice guidelines from the AABB: red blood cell transfusion thresholds and storage. JAMA. 2016;316(19):2025–35.
7. Carson JL, Triulzi DJ, Ness PM. Indications for and adverse effects of red-cell transfusion. N Engl J Med. 2017;377(13):1261–72.
8. Marinakis S, Van der Linden P, Tortora R, Massaut J, Pierrakos C, Wauthy P. Outcomes from cardiac surgery in Jehovah's witness patients: experience over twenty-one years. J Cardiothorac Surg. 2016;11(1):67.
9. Vasques F, Kinnunen EM, Pol M, Mariscalco G, Onorati F, Biancari F. Outcome of Jehovah's Witnesses after adult cardiac surgery: systematic review and meta-analysis of comparative studies. Transfusion. 2016;56(8):2146–53.
10. Mazer CD, Whitlock RP, Fergusson DA, Hall J, Belley-Cote E, Connolly K, et al. Restrictive or liberal red-cell transfusion for cardiac surgery. N Engl J Med. 2017;377(22):2133–44.

11. Hogervorst EK, Rosseel PM, van de Watering LM, Brand A, Bentala M, van der Bom JG, et al. Intraoperative anemia and single red blood cell transfusion during cardiac surgery: an assessment of postoperative outcome including patients refusing blood transfusion. J Cardiothorac Vasc Anesth. 2016;30(2):363–72.
12. Beliaev AM, Marshall RJ, Smith W, Windsor JA. Treatment monitoring and mortality risk adjustment in anaemic Jehovah's Witnesses. ANZ J Surg. 2013;83(3):161–4.
13. Chigbu B, Onwere S, Kamanu C, Aluka C, Okoro O, Feyi-Waboso P, et al. Lessons learned from the outcome of bloodless emergency laparotomies on Jehovah's Witness women presenting in the extremis with ruptured uterus. Arch Gynecol Obstet. 2009;279(4):469–72.
14. Carson JL, Brooks MM, Abbott JD, Chaitman B, Kelsey SF, Triulzi DJ, et al. Liberal versus restrictive transfusion thresholds for patients with symptomatic coronary artery disease. Am Heart J. 2013;165(6):964–71.e1.
15. Levels of evidence and grades of recommendations. Oxford Centre for Evidence Based Medicine. Available at: http://cebm.jr2.ox.ac.uk/docs/old_levels.Htm.
16. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17:1–12.
17. Wells G, Shea B, O'Connell D, Robertson J, Peterson J, Welch V, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses; 2011. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
18. Goldet G, Howick J. Understanding GRADE: an introduction. J Evid Based Med. 2013;6:50–4.