

Review Point

Anemia and transfusion of red blood cells

Anemia y transfusión de glóbulos rojos

Armando Cortés Buelvas

Pathology Department in the School of Health, Universidad del Valle

Armando Cortés Buelvas. Anemia and transfusion of red blood cells. *Colomb.Med.*2013;44 (4):236-41

Article history:

Received: Oct 30-2013

Received in revised form:

Nov-15-2013

Accepted: Dec-30-2013

Keywords: anaemia; blood transfusion; transfusion practice

Palabras Clave: anemia, transfusión sanguínea, práctica transfusional

Abstract

The red cells transfusion is a mainstay in the treatment of anemic patients. These blood transfusions are not without risks. The risk-benefit profile for red cell transfusions to treat anaemia is uncertain, but they may contribute to adverse patient outcomes in some situations. The ability of a patient to tolerate anaemia depends on their clinical condition and the presence of any significant co-morbidity; maintenance of circulating volume is of paramount importance. There is no universal transfusion trigger. Advances in the development and validation of physiological, accessible, practical and reliable markers to guide therapy are expected. To improve patients' outcomes, further study is required to more fully explore the risk of anemia, optimal hemoglobin level, and the risk and efficacy of RBC transfusion. Future clinical investigations with high priority should determine the efficacy of transfusion in those classified as uncertain scenarios. In the absence of data, it is prudent that transfusion is administered with caution in these clinical scenarios.

Resumen

La transfusión de glóbulos rojos es uno de los pilares en el tratamiento de pacientes anémicos. Las transfusiones de sangre no están libres de riesgo. Aunque es incierta la relación riesgo-beneficio de las transfusiones para tratar la anemia, estas pueden ocasionar resultados adversos de los pacientes en algunas situaciones. La capacidad de un paciente para tolerar la anemia depende de su estado clínico y la presencia de cualquier co-morbilidad significativa; la preservación del volumen circulante es de suma importancia. No existe un indicador automático universal para la transfusión. Se espera que los avances en el desarrollo y validación de marcadores fisiológicos, accesibles, prácticos y confiables permitan guiar la terapia. Para mejorar los resultados de los pacientes, se requieren más estudios que exploren más a fondo el riesgo de la anemia, el nivel de hemoglobina óptima, y el riesgo y la eficacia de la transfusión de glóbulos rojos. Las investigaciones clínicas futuras con alta prioridad deben determinar la eficacia de la transfusión en los clasificados como escenarios inciertos. Ante la falta de datos, es prudente que la transfusión se administre con precaución en estos escenarios clínicos.

*Corresponding Author.

E-mail Address: acortes59@gmail.com (Cortés A)

Introduction

Red blood cell (RBC) transfusions are a mainstay in the treatment of anemic patients, making it the most common medical procedure in hospitalized patients¹.

Most RBC transfusions (RBCT) are prescribed for patients with relatively low levels of hemoglobin (Hb) and only in controlled situations. The underlying thinking is that the transfusion will increase oxygen transport and therefore decrease deficiencies thus “relieving” tissue hypoxia. However, this hypothetical benefit of RBC transfusions has not been unequivocally demonstrated.

An inadequate supply of oxygen to tissues can lead to multiple organ failure and increased morbidity and mortality. These deleterious effects appear only with very low Hb levels when compensatory mechanisms do not work properly or are insufficient; however, that level is not exactly known.

The risks and complications of RBCT include: the transmission of infectious diseases, immune suppression, acute respiratory distress syndrome, circulatory overload and errors in administration. With these potential or actual adverse effects taken together with the large variability in observed prescriptions, it has been determined that when faced with “liberal” or “defensive” traditional transfusion criteria, more restrictive transfusion practices are adopted along with an enhanced usage of alternative treatments. However, we must be cautious because this trend can lead us to expose patients unnecessarily to risks of anemia and hypoxia by not administering transfusions.

This makes it essential to specify an appropriate risk/benefit ratio for the transfusion. This is because it is also not permissible to subject the patient to an intervention whose effectiveness has not been documented in terms of reduced mortality or morbidity.

In the 1988 Consensus Conference of the NIH (National Institute of Health) the lack of justification for “classic” transfusion practice was highlighted and it was concluded that “the available evidence does not support the use of a single criterion for transfusion, such as Hb <100 g/L. No single measure can replace good clinical judgment as the basis for decision making concerning RBCT”².

Weiskopf asserts that although millions of units of red blood cells are transfused, the biological effectiveness of this measure has not been demonstrated in prospective, controlled studies, nor do other criteria exist by which one could judge the effectiveness of the transfusion of concentrated red blood cells³.

After almost a century of the clinical use of RBCT, the continued use of this form of therapy is now being questioned. This is not necessarily due to adverse effects, but to the lack of studies that document its effectiveness.

A recent systematic review of the literature considered the results of 45 cohort studies with 272,596 patients in critical condition and revealed that in 42 of the 45 studies transfusion represented greater risk than benefit to patients and in the transfused cohort it presented a higher rate of adverse events than it did to those not receiving transfusions⁴.

Similarly, in clinical randomized controlled trials (RCTs) evaluating the efficacy/ effectiveness of RBCT⁵⁻⁸ it is indicated that the restriction of RBCT in patients without hemorrhage has no significant negative effect on patient outcomes, and it may even improve the results among some populations. Taken together, these studies suggest that RBCT provides minimal benefit for critically ill patients with hemoglobin (Hb) levels greater than 8-9 g/dL⁹⁻¹². Additionally, it may contribute many undesirable results in many clinical situations, with increased morbidity, mortality and length of hospital stay¹³⁻¹⁹.

These findings oblige a more judicious use among the many patients who are routinely transfused. A greater effort should be made to understand that there is a transition point at which the physiological mechanisms fail to compensate for the decreased oxygen supply associated with anemia, in which case transfusion favors the results.

Factors to consider in the analysis

It has been noticed that in young, alert, healthy adults when subjected to an isovolemic hemodilution with a decreased hemoglobin concentration of 12.5 g/dL to 4.8 g/dL that an increased heart rate, systolic volume index and the cardiac index is produced with no systemic evidence of hypoxic changes despite a reduction in the DO₂ (oxygen delivery) to a level of 7.3 mL/kg/min²⁰.

A study conducted with septic patients suggests that the critical DO₂ could be 3.8 mL/kg/min²¹.

The decrease in DO₂ with anemia does not always translate into decreased VO₂ (oxygen consumption) due to the intervention of compensatory physiological mechanisms, such as the increase in cardiac output and tissue O₂ extraction. The VO₂ is, in turn, balanced by the ability of peripheral tissues to modify oxygen extraction (EO₂) in hypoxemic states thus altering micro-vascular blood flow and maintaining a stable tissue pO₂²².

The studies that reveal a lack of increased tissue O₂ with RBCT have been interpreted as a lack in transfusion effectiveness and are attributed to the loss of 2,3-diphosphoglycerate and nitric oxide during storage or to increased viscosity^{23,24}.

Cardiac function determines the clinical tolerance limit to anemia in any patient. Oxygen delivery to the myocardium increases only by means of improving the blood flow in the coronary arteries²⁵.

The consequent reduction of coronary flow can thus increase the pressure at the end of the diastole, to produce changes in the ECG and subsequent symptomatic ischemia²⁶.

Some studies in humans have thrown light on the limits of physiological compensation of anemia. The critical Hb at rest has been estimated at approximately 20-25% of normal Hb²².

The first report was documented in an 84 year old Jehovah's Witness who refused transfusion and died after surgery with a Hb of 1.6 g/dL. The critical DO₂ in this patient under anesthesia was 4.9 mL O₂/kg/min for a VO₂ of 2.4 mL O₂/kg/min and death occurred at

a Hb level of 4.0 g/dL. The dissociation curve of oxyhemoglobin, after correction for changes in the pH and PCO_2 , deviates to the right with a hematocrit of 8%. This indicates a decrease in oxygen affinity of hemoglobin as a compensatory mechanism to facilitate the delivery of O_2 to peripheral tissues in extreme anemia²⁷.

Furthermore, in critically ill patients sedated after cessation of life support, the DO_2 varies between 3.8-4.5 mL O_2 /kg/min. For a VO_2 of 2.4 mL O_2 /kg/min, the critical EO_2 was approximately 60%²¹.

Considering that the critical DO_2 varies with different metabolic requirements, subsequent studies were carried out taking measurements during states of consciousness in which the VO_2 is higher. It has been shown that healthy humans at rest are able to tolerate acute isovolemic hemodilution with a Hb of 5 g/dL²⁷ -although a slight reduction in alertness occurs which is reversible^{28,29}.

In 32 conscious individuals at rest, no significant change was produced any in the concentration of lactate or VO_2 despite the decrease in DO_2 during progressive isovolemic hemodilution with 5% albumin and/or autologous plasma to a level of Hb 5 g/dL³⁰.

In another study with conscious young healthy volunteers it was found that for a VO_2 of 3.4 mL O_2 /kg/min, the critical DO_2 during acute hemodilution with 5% albumin and autologous plasma was less than 7.3 mL O_2 /kg/min and 4.8 g/dL of Hb²⁰.

However, in the presence of coronary artery disease, the Hb threshold may increase. In animal models it has been reported that Hb threshold may be at a level of 7-7.5 g/dL in the presence of coronary artery stenosis with limited tolerance to isovolemic hemodilution^{31,32}.

Contractile dysfunction induced by ischemia and compromise in the delivery and consumption of O_2 can be reversed and corrected with RBCT by increasing the Hb to 1.9 g/dL³¹.

The results of these and other experimental studies, however, are not easily extrapolated to clinical situations for patients with comorbidities and changes in the balance of supply and demand of oxygen.

Bases for the decision

Currently, "the transfusion threshold" is based on predetermined values for Hb concentrations that are derived from a few randomized clinically controlled trials, various observational cohort studies, or from the opinion of experts^{33,34}. This implies the existence of a Hb threshold level below which the transfusion should be initiated; a threshold that remains uncertain with current testing methods and the analysis of multiple observational studies and a few randomized controlled trials (RCTs)³⁵. Unfortunately, the decision is also influenced by regulations, fear of future litigation, and public expectations more than clinical evidence³⁶.

Two concepts form the basis for the use of the Hb concentration as a determinant of RBCT: the optimal level of Hb and the minimum acceptable level of Hb. The optimal level of Hb is the concentration of Hb at which organic functionality is maximal. Studies carried

out on individuals undergoing acute normovolemic hemodilution, found that oxygen transport (TO_2) reaches a maximum at a 30% Hct (Hb 100 g/L), and it decreases as hemodilution and hemoconcentration progress. In diverse experimental animal models it has been shown that TO_2 and survival are optimal at an Hct between 30 to 40%.

The minimum acceptable level of Hb is that point at which coronary blood flow cannot increase sufficiently to meet the oxygen demands of the myocardium. The minimum acceptable level of Hb should be considered as the transfusion threshold, but this level has yet to be clearly defined. While individuals with cardio-respiratory disease may need to maintain Hb levels >90-100 g/L to prevent signs of myocardial ischemia, healthy individuals with normal compensatory mechanisms can tolerate chronic levels of Hb from 50-60 g/L that maintains the blood volume.

That is, one should try to optimize the cardio-pulmonary hemodynamic in patients before making the decision to transfuse. In many of them an improvement in cardiac dynamics and supra-maximal O_2 delivery can be achieved by increasing the concentration of inspired O_2 , correction of blood volume, the postoperative treatment of pain, etc.

Using the estimated volume of bleeding as a determinant of RBCT has two drawbacks: on the one hand, it is often difficult to determine and, in fact, at least in specific surgeries, the actual blood loss can be almost double that observed³⁷. Also, the effects of bleeding will depend on factors such as the previous Hb, the circulating volume for the individual (which, in turn, depends on weight, height and sex), the rate of bleeding or the quality of volume replacement.

However, given that in the evaluation of the effects of anemia from acute blood loss are the critical factors of volume and rate of blood loss, as well as the degrees of hemodynamic instability. These all may be indicative of the need to transfuse. When losses are very rapid, in spite of volume replacement and hemodynamic stabilization of the patient, RBCT will very likely be needed to restore the O_2 transport capacity, particularly in cases of severe trauma. Similarly, if the volume of bleeding is less than 25% of volume RBCT may rarely be necessary; between 25% and 50% may be frequently required, while acute loss of over 50% is almost always fatal.

The utility of the metabolic markers of hypoxia as determinants of RBCT is also limited. Lactate is produced in many hypoxic tissues as the end product of glycolysis under anaerobic conditions with peak plasma concentrations >2 mEq/L. However, the use of this metabolite as the only marker of tissue hypoxia, and therefore as a determinant for RBCT shows serious limitations from being influenced by the circulatory state, liver function, or concomitant sepsis. Thus, in a group of individuals under forty years of age, who are conscious and at rest and without cardiovascular, lung or liver disease, non-smokers who not taking medication effecting cardiovascular function, a decreased Hb level up to 50 g/L from acute normovolemic hemodilution did not result in an inadequate O_2 transport to the tissues as there was no change in either O_2 consumption or plasma lactate concentration³⁰.

On the other hand, the results of this study are consistent with those obtained in patients with acute myocardial infarction or sepsis in which no correlation was found between the levels of lactate and oxygen supply. Moreover, in any case, such a correlation would only indicate an overall change in oxygen supply but would not provide specific information on regional hypoxia.

The arterio-venous difference in the partial pressure of CO₂ (P_{a-v}CO₂) can be a useful but nonspecific parameter for determining the presence of tissue hypoxia, especially in the post-operative setting of certain surgeries. After coronary artery bypass surgery, the P_{a-v}CO₂ is influenced by the metabolic rate, body temperature (possibly due to the release of CO₂ during re-warming the patient) and decreased pulmonary elimination of CO₂. In these circumstances, patients with abnormally elevated P_{a-v}CO₂ show a greater incidence of post-operative complications from tissue hypoxia (low cardiac output, arrhythmias, prolonged extubation, increased blood creatinine, jaundice)³⁸.

The oxygen extraction quotient (CEO₂) is the relationship between the consumption and delivery of O₂ (VO₂/DO₂). It is expressed in percentages and indicates the percentage of O₂ provided that has been utilized. Normal CEO₂ is 25%. Some studies of normovolemic anemia performed with different animals have focused on the study of CEO₂ as a good indicator of when to perform the T. Its application to daily clinical practice is lacking.

Although the only actual reason for establishing an indication for RBCT is for maintaining the O₂ transport capacity, it does not always have the means to determine the transport capacity of O₂ (e.g., SvO₂, TO₂, VO₂, gastric pH_i, blood lactate) and it is very difficult to know the time at which each patient needs to increase their transport capacity. This is especially so when you consider that their oxygen needs pre-operatively, during the intervention, and post-operatively are quite different.

Once anesthetized, the patient is in a state of minimal metabolic demand. If young, healthy individuals get adequate TO₂ with Hb levels around 50 g/L, this same number should be applicable to individuals ASA I anaesthetized in which O₂ consumption is lower than while at rest. Overall, general anesthesia with neuromuscular blockage and mechanical ventilation decreases oxygen consumption by 20-40%, which can make the critical TO₂ descend to a lower level than in the conscious individual³⁹.

In contrast, O₂ demands increase during the post-anesthetic recovery and VO₂ multiplies by a factor of 2-3, depending on the type of anesthesia used, the aggressiveness of the surgery, the degree of post-operative analgesia in the presence of pain and characteristics of the patient. Again, this situation, which is generally well-tolerated by young and healthy patients with active compensating mechanisms for anemia, may be post-operatively complicated by a compromised cardiovascular function, or among patients with sepsis, especially if they are elderly. A recent review⁴⁰ concludes that due to the tremendous existing variability among patients with respect to delivery and extraction of O₂ and cardiac reserve, the critical level of Hb has an individual value as there is no general threshold for RBCT. Given the evidence that myocardial ischemia is a critical factor in the patient's ability to tolerate anemia, no patient over forty years of age with Hb <100

g/L should undergo elective surgery without previously ruling out myocardial ischemia.

The effectiveness of the RBCT can only be established by results from well-designed randomized clinical trials. Until now the clinical trials conducted to compare two transfusion strategies ("restrictive" and "liberal") in different types of patients have not shown significant differences in terms of morbidity, mortality and functional status of patients, with the possible exception of those with AMI or unstable angina.

Transfusion criteria

As previously noted, at the 1988 Consensus Conference organized by the U.S. National Institute of Health the threshold concentration of hemoglobin (Hb) from consensus was set at 70 g/L. It was emphasized that there was a direct call to establish needs and clinical symptoms as the basis for the transfusion decision, and not base the decision solely on Hb concentrations. That is, to transfuse if Hb <70 g/L, to individualize the decision for Hb levels of 70-100 g/L and not to transfuse if Hb > 100 g/L. Since then, several guidelines have been published, the result of other Consensus Conferences along the same lines; that is, the reasons for the use of "restrictive" transfusion criteria prevailed over those more "liberal".

In the field of intensive care, in a multi-centric, randomized, prospective study, Transfusion Requirements in Critical Care (TRICC), the mortality rate in critically ill patients undergoing a "restrictive" RBCC protocol (Hb <70 g/L to keep it between 70 and 90 g/L) was compared with "liberal" criteria (Hb <100 g/L, to keep it between 100 and 120 g/L)⁵. The results of this study indicated that there was no difference in mortality when the two subgroups of patients with significant cardiac disease were compared.

However, according to the subsequent analysis of the TRICC study data⁴¹ variations in mortality rate after thirty days were found and opposite in the "liberal" group when compared to the mortality rate in the "restrictive" group, according to the presence or absence of coronary artery disease before randomization.

In subjects with ischemic heart disease, mortality was greater in the restrictive group than in the liberal group (26% versus 21%, respectively); whereas in patients without ischemic heart disease, mortality was lower in the restrictive group than in the liberal group (16% versus 25%, respectively) (Breslow-Day test, $p=0.03$).

This analysis seems to demonstrate that the results of TRICC may be strongly influenced by the presence of non-comparable groups with different transfusion practices and are inadequate in each study group. The excess risk incurred by each of these subgroups makes comparing global mortality rates between the two transfusion strategies studied hard to interpret.

Given that the studies published before the TRICC indicated that clinicians used higher transfusion thresholds in patients with ischemic heart disease than in younger subjects with less comorbidity, none of the study groups represents the usual practice.

In euvolemic surgical patients, almost all randomized studies to date have shown that the use of a "restrictive" transfusion threshold does not cause an increase in mortality or morbidity

or in the duration of the hospital stay, while reducing both the percentage of patients transfused and the volume of allogeneic blood administered⁴²⁻⁴⁸.

The exception is from the work of Foss *et al.*, but it was not designed to evaluate this objective and it lacked the statistical power to evaluate it⁴⁹.

The recommendations of the AABB formulated in accord with the criteria of the GRADE methodology (Grades of Recommendation, Assessment, Development, and Evaluation), recently published are as follows⁵⁰:

Recommendation 1: The AABB recommends adhering to a restrictive transfusion strategy (7-8 g/dL) in hospitalized, stable patients (GRADE 1A: strong recommendation, high quality evidence).

Recommendation 2: The AABB suggests adhering to a restrictive strategy in hospitalized patients with a preexisting cardiovascular disease and consider transfusion in patients with symptoms or a hemoglobin of 8 g/dL or less (GRADE 2B: weak recommendation, moderate quality evidence).

Recommendation 3: The AABB cannot make a recommendation for or against the use of a liberal transfusion threshold or a restrictive one, for hospitalized patients, hemodynamically stable with acute coronary syndrome (GRADE 0: unclear recommendation, very low quality evidence).

Recommendation 4: The AABB suggests that transfusion decisions be based on the symptoms, as well as on hemoglobin concentrations (GRADE 2C: Weak recommendation, low quality evidence).

Conclusions and recommendations

Red blood cells transfusions is widely used in the treatment of anemia, although adequate thresholds for its use remain controversial. Although therapeutic modalities should be subject to a rigorous evaluation of its efficacy and safety prior to use in clinical practice, RBCT has not been subjected to a similar examination. Besides the already known complications from transfusions, numerous studies indicate that RBCT may be associated with unfavorable outcomes.

The few conclusive results and non-controversial data have not overcome the difficulties that have prevented previous attempts to establish a policy or guide for RBCT. Despite these limitations and the lack of definitive answers, doctors often have no other choice but the consensus guidelines³⁴.

In building a "standard of care" consensus guidelines and reviews often do not represent the actual current clinical practice, and several examples illustrate its ineffectiveness in modifying clinical practice⁵¹⁻⁵⁴.

Almost two thirds of physicians report regularly transfusing RBC in probably unnecessary situations,⁵⁵ and there is wide variation

in transfusion practices with respect to weight that is attributed to clinical factors used in decision making, which also hinders the characterization of current practice⁵⁶. A high priority for future clinical investigations should be determining the efficacy of RBCT in those situations classified as uncertain. In the absence of data, it is prudent that RBCT be administered with caution in these clinical scenarios. Therefore, we should do it on an individual basis, i.e., carefully weighing the risks of anemia and the risks and benefits to be derived from each of these products for each patient, supporting them with the proper dosage and monitoring the expected therapeutic response, simultaneously with the application of an appropriate alternative to RBCT and efficient for our patient at all times. That is, we must seek the maximum benefit with the least possible exposure.

References

1. AABB. The 2007 national blood collection and utilization survey report. <http://www.aabb.org/programs/biovigilance/nbcus/Documents/07nbcusrpt.pdf>. Accessed 15 April 2011.
2. Perioperative Red Cell Transfusion. NIH Consens Dev Conf Consens Statement. 1988; 7(4): 1-19.
3. Weiskopf RB. Do we know when to transfuse red cells to treat acute anemia?. *Transfusion* 1998; 38: 517-21.
4. Marik PE, Corwin HL. Efficacy of red blood cell transfusion in the critically ill: a systematic review of the literature. *Crit Care Med*. 2008; 36: 2667-74.
5. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, *et al.* A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion requirements in critical care investigators, Canadian Critical Care Trials Group. *N Engl J Med*. 1999; 340: 409-17.
6. Hebert PC, Yetisir E, Martin C, Blajchman MA, Wells G, Marshall J, *et al.* Is a low transfusion threshold safe in critically ill patients with cardiovascular diseases? *Crit Care Med*. 2001; 29: 227-34.
7. Lacroix J, Hebert PC, Hutchison JS, Hume HA, Tucci M, Ducruet T, *et al.* Transfusion strategies for patients in pediatric intensive care units. *N Engl J Med*. 2007; 356: 1609-19.
8. Carson JL, Terrin ML, Magaziner J, Chaitman BR, Apple FS, Heck DA, *et al.* LBA-6 Transfusion trigger trial for functional outcomes in cardiovascular patients undergoing surgical hip fracture repair (FOCUS): The principle results. Paper presented at the 51st Annual Meeting of the American Society of Hematology, December 5-9, 2009.
9. Napolitano LM, Corwin HL. Efficacy of red blood cell transfusion in the critically ill. *Crit Care Clin*. 2004; 20: 255-68.
10. Madjdpour C, Spahn DR. Allogeneic red blood cell transfusion: Physiology of oxygen transport. *Best Pract Res Clin Anaesthesiol*. 2007; 21: 163-71.

11. Vincent JL, Sakr Y, De Backer D, Van der Linden P. Efficacy of allogeneic red blood cell transfusions. *Best Pract Res Clin Anaesthesiol.* 2007; 21: 209-19.
12. Fernandes CJ Jr, Akamine N, De Marco FV, De Souza JA, Lagudis S, Knobel E. Red blood cell transfusion does not increase oxygen consumption in critically ill septic patients. *Crit Care.* 2001; 5: 362-7.
13. Corwin HL, Gettinger A, Pearl RG, Fink MP, Levy MM, Abraham E, *et al.* The CRIT study: anemia and blood transfusion in the critically ill—current clinical practice in the United States. *Crit Care Med.* 2004; 32: 39-52.
14. Vincent JL, Baron JF, Reinhart K, Gattinoni L, Thijs L, Webb A. *et al.* Anemia and blood transfusion in critically ill patients. *JAMA.* 2002; 288: 1499-507.
15. Hill GE, Frawley WH, Griffith KE, Forestner JE, Minei JP. Allogeneic blood transfusion increases the risk of postoperative bacterial infection: a meta-analysis. *J Trauma.* 2003; 54: 908-14.
16. Palmieri TL, Caruso DM, Foster KN, Cairns BA, Peck MD, Gamelli RL. *et al.* Effect of blood transfusion on outcome after major burn injury: A multicenter study. *Crit Care Med.* 2006; 34: 1602-7.
17. Stone TJ, Riesenman PJ, Charles AG. Red blood cell transfusion within the first 24 hours of admission is associated with increased mortality in the pediatric trauma population: A retrospective cohort study. *J Trauma Manag Outcomes.* 2008; 2: 9-13.
18. Marik PE, Corwin HL. Efficacy of red blood cell transfusion in the critically ill: a systematic review of the literature. *Crit Care Med.* 2008; 36: 2667-74.
19. Vamvakas EC, Blajchman MA. Transfusion-related mortality: the ongoing risks of allogeneic blood transfusion and the available strategies for their prevention. *Blood.* 2009; 113: 3406-17.
20. Lieberman JA, Weiskopf RB, Kelley SD, Feiner J, Noorani M, Leung J, Toy P. *et al.* Critical oxygen delivery in conscious humans is less than 7.3 ml O₂. kg⁻¹. min⁻¹. *Anesthesiology.* 2000; 92:407-13.
21. Ronco JJ, Fenwick JC, Tweeddale MG, Wiggs BR, Phang PT, Cooper DJ. *et al.* Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic humans. *JAMA.* 1993; 270: 1724-30.
22. Klein H, Spahn D, Carson J. Red blood cell transfusion in clinical practice. *Lancet.* 2007; 370: 415-26.
23. Madjdpour C, Spahn D. Allogeneic red blood cell transfusions: Efficacy, risks, alternatives and indications. *Br J Anaesthesiol.* 2005; 95: 33-42.
24. Madjdpour C, Spahn D, Weiskopf R. Anemia and perioperative red blood cell transfusion: A matter of tolerance. *Crit Care Med.* 2006; 34: S102-S8.
25. Gerber D. Transfusion of packed red blood cells in patients with ischemic heart disease. *Crit Care Med.* 2008; 36: 1068-74.
26. Nohara R. Diagnosis with O₂ kinetics. Old but new. *Circulation J.* 2009; 73: 1795-6.
27. Van Woerkens EC, Trouwborst A, van Lanschot JJ. Profound hemodilution: what is the critical level of hemodilution at which oxygen delivery-dependent oxygen consumption starts in an anesthetized human?. *Anesth Analg.* 1992; 75: 818-21.
28. Weiskopf RB, Feiner J, Hopf HW, Viele MK, Watson JJ, Kramer JH. *et al.* Oxygen reverses deficits of cognitive function and memory and increased heart rate induced by acute severe isovolemic anemia. *Anesthesiology.* 2002; 96: 871-7.
29. Weiskopf RB, Feiner J, Hopf H, Lieberman J, Finlay HE, Quah C. *et al.* Fresh blood and aged stored blood are equally efficacious in immediately reversing anemia induced brain oxygenation deficits in humans. *Anesthesiology.* 2006; 104: 911-20.
30. 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: 217-21.
31. Spahn DR, Smith LR, Veronee CD, McRae RL, Hu WC, Menius AJ, *et al.* Acute isovolemic hemodilution and blood transfusion. Effects on regional function and metabolism in myocardium with compromised coronary blood flow. *J Thorac Cardiovasc Surg.* 1993; 105: 694-704.
32. Levy PS, Kim SJ, Eckel PK, Chavez R, Ismail EF, Gould SA, *et al.* Limit to cardiac compensation during acute isovolemic hemodilution: influence of coronary stenosis. *Am J Physiol.* 1993; 265: H340-9.
33. Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris VA, Ferraris SP, Saha SP, Hessel EA 2nd, Haan CK, *et al.* Perioperative blood transfusion and blood conservation in cardiac surgery: The Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists Clinical Practice Guideline. *Ann Thorac Surg.* 2007; 83: s27-86.
34. Napolitano LM, Kurek S, Luchette FA, Corwin HL, Barie PS, Tisherman SA, *et al.* Clinical practice guideline: Red blood cell transfusion in adult trauma and critical care. *Crit Care Med.* 2009; 37(12): 3124-57.
35. Wang J, Klein H. Red blood cell transfusion in the treatment and management of anaemia: The search for the elusive transfusion trigger. *Vox Sang.* 2010; 98: 2-11.
36. Vamvakas EC. Evidence-based practice of transfusion medicine: Is it possible and what do the words mean?. *Transfus Med Rev.* 2004; 18: 267-78.
37. Sehat KR, Evans R, Newman JH. How much blood is really lost in total knee arthroplasty?. Correct blood loss management should take hidden loss into account. *Knee.* 2000; 7:151-5.

38. Cavaliere F, Martinelli L, Guarnieri S, Varano C, Rossi M, Schiavello R. Arterial-venous PCO₂ gradient in early postoperative hours following myocardial revascularization. *J Cardiovasc Surg.* 1996; 37: 499-503.
39. Carson JI, Chen AY. In search of the transfusion trigger. *Clin Orthop.* 1998; 357: 30-5.
40. Lundsgard-Hansen P. Safe hemoglobin or hematocrit levels in surgical patients. *Worl J Surg.* 1996; 20: 1182-8.
41. Deans K, Minneci PC, Suffredini AF, Danner RL, Hoffman WD, Ciu X, *et al.* Randomization in clinical trials of titrated therapies: Unintended consequences of using fixed treatment protocols. *Crit Care Med.* 2007; 35: 1509-16.
42. Grover M, Talwalkar S, Casbard A, Boralessa H, Contreras M, Boralessa H, *et al.* Silent myocardial ischaemia and haemoglobin concentration: a randomized controlled trial of transfusion strategy in lower limb arthroplasty. *Vox Sang.* 2006; 90: 105-12.
43. Murphy GJ, Rizvi S, Battaglia F, Culliford L, Rogres C, Cohen A, *et al.* A pilot randomised controlled trial of the effect of transfusion threshold reduction on transfusion rates and morbidity after cardiac surgery. Society for Cardiothoracic Surgery in Great Britain and Ireland. Annual meeting 2007; 94. [http://www.scts.org/documents/PDF/FinalPrinted Programme24Feb2007.pdf](http://www.scts.org/documents/PDF/FinalPrinted%20Programme24Feb2007.pdf).
44. Slight RD, O'Donohoe P, Fung AKY, Alonzi C, McClelland DBL, Mankad PS. Rationalizing blood transfusion in cardiac surgery: the impact of a red cell volume-based guideline on blood usage and clinical outcome. *Vox Sang.* 2008; 95: 205-10.
45. Haijar LA, Vincent JL, Galas FRBG, Nakamura RE, Silva CMP, Santos MH, *et al.* Transfusion requirements after cardiac surgery. The TRACS randomized controlled trial. *JAMA.* 2010; 304: 1559-67.
46. Willems A, Harrington K, Lacroix J, Biarent D, Joffe AR, Wensley D, *et al.* Comparison of two red-cell transfusion strategies after pediatric cardiac surgery: a a subgroup analysis. *Crit Care Med.* 2010; 38: 649-56.
47. Rouette J, Trottier H, Ducruet T, Beaunoyer M, Lacroix J, Tucci M. *et al.* Red blood cell transfusion threshold in postsurgical pediatric intensive care patients. A randomized clinical trial. *Ann Surg.* 2010; 251: 421-7.
48. Carson JL, Terrin ML, Noveck H, Sanders DW, Chaitman BR, Rhoads GG, *et al.* Liberal or restrictive transfusion in high-risk patients after hip surgery. *N Engl J Med.* 2011; 365: 2453-62.
49. Foss NB, Kristensen MT, Jensen PS, Palm H, Krasheninnikoff M, Kehlet H. The effects of liberal versus restrictive transfusion thresholds on ambulation after hip fracture surgery. *Transfusion.* 2009; 49: 227-34.
50. Carson JL, Grossman BJ, Kleinman S, Tinmouth AT, Marques MB, Fung MK, *et al.* Red blood cell transfusion: a clinical practice guideline from the AABB. *Ann Intern Med.* 2012; 157(1):49-58.
51. Kosecoff J, Kanouse DE, Rogers WH, McCloskey L, Winslow CM, Brook RH. Effects of the national institutes of health consensus development program on physician practice. *JAMA.* 1987; 258: 2708-13.
52. Lomas J, Anderson GM, Domnick-Pierre K, Vayda E, Enkin MW, Hannah WJ. Do practice guidelines guide practice? The effect of a consensus statement on the practice of physicians. *N Engl J Med.* 1989; 321: 1306-11.
53. Hill MN, Levine DM, Whelton PK. Awareness, use, and impact of the 1984 Joint National Committee consensus report on high blood pressure. *Am J Public Health.* 1988; 78: 1190-4.
54. Eisenstaedt RS. Modifying physicians' transfusion practice. *Transfus Med Rev.* 1997; 11: 27-37.
55. Salem-Schatz S, Avorn J, Soumerai SB. Influence of clinical knowledge, organizational context, and practice style on transfusion decision making. Implications for practice change strategies. *JAMA.* 1990; 264: 476-83.
56. Brown RL, Brown RL, Edwards JA, Nutz JF. Variation in a medical faculty's decisions to transfuse. Implications for modifying blood product utilization. *Med Care.* 1992; 30(12):1083-96.