Anaemia in the Critically Ill—The Optimal Haematocrit

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Abstract

***Introduction**: The optimal haematocrit for the critically ill patient is undetermined. **Methods**: This review focuses on clinical and experimental papers regarding the aetiology and management of anaemia from the Medline database. Data from our intensive care unit (ICU) were also included. **Results**: Anaemia may result from frequent blood sampling, gastrointestinal bleeding, surgical blood loss, impaired erythropoeitic response, and nutritional deficiencies of iron, vitamin B_{12} and folate. Available data on the minimum tolerated Hct are conflicting. There has been emphasis that transfusions should not be based on a single "trigger". Recent data suggest a linear relationship between Hct and cerebral oxygen delivery (DO_2). There is evidence that anaemia increases the mortality, and the risk is higher in patients with cardiovascular disease. Conversely, transfusions are not without risks, which include transmission of infections, incompatibility reactions and immunomodulation. Restricting blood transfusion has been shown to result in lower 30-day mortality in certain patient groups. Minimising blood loss and nutritional support are important. Alternative strategies to transfusion include erythropoeitin and blood substitutes like cell-free haemoglobin, perfluorocarbon emulsions and liposome-encapsulated Hb. Hyperbaric oxygen has also been tried. **Conclusion**: Oxygen consumption requires oxygen delivery. Haematocrit delivers oxygen. However, if oxygen delivery is not limited by haematocrit or is achieved by other means, then the concept of the optimal haematocrit is irrelevant. There are currently no guidelines for the management of anaemia in the critically ill.*

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Key words: Blood substitutes, Blood transfusion, Erythropoeitin, Haemoglobin, Oxygen delivery

Physiology and Aetiology

The function of haemoglobin (Hb) is to transport oxygen to the tissues. Approximately 97% of oxygen is transported via Hb, while 3% is transported dissolved in the plasma. The main function of erythrocytes is being a carrier for Hb. The red cell lifespan is approximately 120 days; hence constant replacement of circulating red cells by erythropoiesis is required. The haematocrit (Hct) is measured as the ratio of the volume of the red cells to the volume of the blood sample. Although Hb is measured independently, Hb is mathematically the product of Hct with mean corpuscular haemoglobin concentration (MCHC). In the absence of diseases altering MCHC grossly, Hct and Hb are essentially proportional to one another. Anaemia is variously defined as Hct <36% or Hb <120g.L^{-1}, with minor variation with sex and age. At levels below these, erythropoietin (EPO) levels increase exponentially.

In our intensive care unit (ICU), the incidence of patients with a Hct <36% on admission was 75% (Fig. 1). This compares with quoted incidences of 77%.[1] Important causes of anaemia in the critically ill patient include frequent blood sampling, bleeding from the gastrointestinal tract, surgical blood loss, inappropriately low EPO, and nutritional deficiencies of iron, vitamin B_{12} and folate.

Early data implicated phlebotomy as a significant factor.[2] In patients who stayed more than 7 days in the ICU, the equivalent of 30% of the total blood transfused was phlebotomised. Patients who did not require blood transfusion had been phlebotomised significantly less than those who were transfused, and had lower mortalities and lengths of stay. Multiple regression analysis found that phlebotomy was the only predictive factor for blood transfusion, explaining 49% of the variations in amount of blood transfused, with no other particular ICU admission variable predicting transfusion. Later studies revealed less blood being drawn for diagnostic purposes,[1] suggesting technical improvements in blood measurements and restraint in excessive blood sampling.[3]

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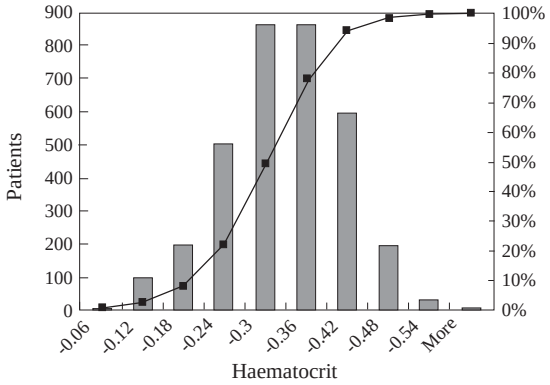

Fig. 1. Haematocrit on admission to ICU PYNEH.

Clinically important bleeding from stress gastritis occurs in 2.8% of ICU patients, and the risk of bleeding increases cumulatively.[4] Interleukin-6, a mediator of the acute phase response, has been found to induce experimental intestinal bleeding.[5] A transferrin saturation <20% had been reported in 50% to 72% of ICU patients, and some patients had folic acid concentrations less than normal.[1] Oral and enteral administration of folate supplies considered to be physiological were inadequate to normalise all blood folate levels in acutely ill patients[6] and significant losses occurred if the patients underwent renal replacement therapy.[7]

The existence of chronic anaemia indicates that the erythropoietic adaptation is either lacking or inadequate. Blunting of the EPO response clearly occurs in critically ill children as well as adults.[8,9] In the presence of renal failure and sepsis, the inverse correlation between Hct and EPO is lost.[9] A number of mediators including interleukin-1α, interleukin-1β, tumour necrosis factor-α, tumour growth factor-β are responsible for inhibiting EPO.

The Concept of the Optimum Hct

Systemic physiological adaptations occurring in anaemia increase oxygen delivery (DO_2). These include increases in cardiac output, a shift of the oxygen dissociation curve to the right, erythropoeisis and increases in oxygen extraction from the blood. In critically ill patients, the compensatory mechanisms may be restricted or cease to function. The rationale of treatment of anaemia is similarly to improve DO_2 to the tissues. In vitro haemodilution of blood flow through glass capillaries revealed that the optimum Hct was 30% to 33% for optimal DO_2.[10] More recent data, however, showed a linear relationship between Hct and cerebral DO_2 with maximal DO_2 occurring at 40% to 45%.[11] Using PET scans and O_2[15] inhalation, it was found that despite the increased cerebral blood flow with haemodilution, cerebral DO_2 decreased, with the optimal Hct being a normal Hct.[12]

However, optimising DO_2 is useful only if it is a limiting factor in oxygen consumption (VO_2). For example, there is unequivocal evidence that induced erythrocythemia improves athletic endurance.[13,14] Athletes have long recognised the use of altitude training to boost their Hct.[15] To determine the optimum Hct in an ICU patient, the crucial issues are whether pathological oxygen supply deficiency exists in the critically ill, and if so, in which ICU patients and what the critical oxygen delivery threshold may be.

The Critical Oxygen Delivery Threshold

In baboons, acute normovolemic haemodilution (ANH) with colloids to a Hct of 20% allowed complete cardiac compensation; at 10% to 20% there was partial compensation and below 10% there was decompensation.[16] ANH to a Hb of 50g.L^{-1} in conscious healthy resting humans did not produce any evidence of inadequate systemic DO_2, using changes in VO_2 and plasma lactate concentration as markers.[17] However, the same group of investigators later showed decreasing energy levels when the Hb was decreased from 70 to 60 to 50 g.L^{-1} in healthy volunteers.[18] They also found subtle increases in reaction time and impaired immediate and delayed memory when the Hb level was dropped to 60 and 50 g.L^{-1}.[19] These changes were reversible with erythrocyte infusion. In young conscious healthy volunteers, using ANH and intravenous esmolol to decrease the DO_2 to 7.3 ml O_2.kg^{-1}.min^{-1}, produced no evidence of inadequate systemic oxygenation. A critical DO_2 was not detected.[20] In an anaesthetised Jehovah's Witness patient, a critical DO_2 of 4.9 ml.kg^{-1}.min^{-1} was found.[21]

In terminally ill ICU patients, critical DO_2 of 3.8 ml.kg^{-1}.min^{-1} and 4.5 ml.kg^{-1}.min^{-1} were found in septic and non-septic patients respectively during withdrawal of therapy.[22] Survival, without long-term consequence in a patient with antepartum haemorrhage with a Hb of 14 g.L^{-1}, has been reported.[23] From our own ICU, an 84-year-old female admitted post gastrointestinal surgery survived to hospital discharge after an ICU stay of 9 days despite an admission Hct of 6%.

Evidence that severe anaemia is well tolerated or adequate does not equate to evidence that this level of Hct is optimum. The safe lower limit of Hb is thus uncertain. Experiences with Jehovah's Witnesses have suggested that Hb levels of 50 g.L^{-1} were safe, though there were limitations to the data presented.[24] The practice guidelines of the American Society of Anesthesiologists stress that blood transfusions should not be dictated by a Hb "trigger", but should be based on the patient's risk of developing complications from inadequate oxygenation.[25] A 1988 Consensus Conference suggested a haemoglobin level of

70 g.L^{-1} was appropriate.[26] This was subsequently lowered to 60 g.L^{-1} in selected cases.[27] Significant regional variation has been noted in the transfusion practices of different physicians.[26]

Anaemia is Detrimental

Cardiovascular responses to anaemia include decreased systemic vascular resistance, decreased blood viscosity, increased heart rate, increased stroke volume index and increased cardiac output. DO_2 is decreased at the lowest Hb levels and oxygen consumption is increased. The compensatory mechanisms of tachycardia and increased stroke volume increase the demands on the myocardium at a time when the oxygen delivery is decreased. Patients with cardiovascular disease have been shown to tolerate anaemia poorly. The incidence of postoperative myocardial ischaemia and morbid cardiac events was higher amongst those with a Hct less than 28%.[28] The relative risk of mortality in patients with cardiovascular disease associated with a low Hb level was consistently higher than in patients without cardiovascular disease.[29]

The relationship between the standardised mortality ratio (observed hospital mortality/APACHE II predicted hospital mortality) and Hct for 3421 patients over 5 years in our ICU is shown in Figure 2. In a 14-year retrospective cohort of 1958 patients aged 18 years and older who underwent surgery and declined blood transfusion for religious reasons, the adjusted odds ratio for post-operative mortality increased with decreasing preoperative Hb.[29] The confounders adjusted for were the APACHE II and age score, the Charlson co-morbidity Index, and cardiovascular disease. Low preoperative Hb and a Hb decline of more than 40 g.L^{-1} increased the risk of death, which was higher in patients with cardiovascular disease. It is unclear if this association implies causality though the data are persuasive. Neither is it clear if subsequent changes in the management of anaemia would have altered mortality. It may be that anaemia is a marker of severity of underlying disease still unaccounted for by the adjustment, or that treatment options were inadequate for anaemic patients. In the US Medicare system, from a haemodialysis patient database now totalling 74,598 patients, Cox regression analysis also revealed increasing mortality with Hct <36%.[30] This data allowed the reimbursement for EPO usage in end stage renal disease (ESRD) patients with Hct <36%, implying an optimum Hct of 36%.

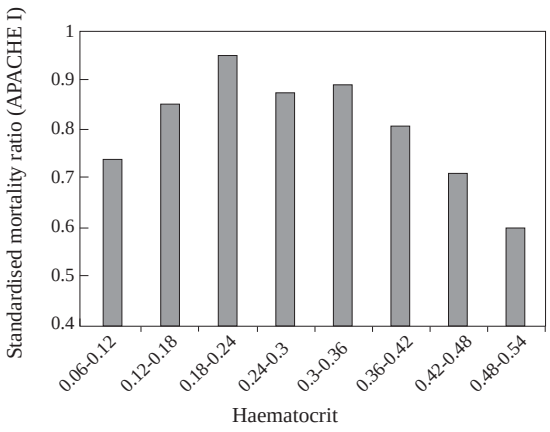

Fig. 2. Relationship between standardized mortality ratio and admission Hct.

A randomised controlled trial (RCT) reported that supranormal oxygen delivery significantly reduced mortality in critical surgical patients.[31] Specifically, a haematocrit of 33% was recommended in the protocol group. There are now 2 other RCTs[32,33] that confirm this result (Table I). There thus appears to be some benefit to increasing oxygen delivery in surgical patients who may undergo surgery. However, a number of other trials in the general ICU population do not support the hypothesis that supranormal oxygen delivery is associated with improved outcomes.[34]

Red Cell Transfusion is Detrimental

Blood transfusions are risky. The incidence of hepatitis C virus seroconversion is reported to be 0.03% per transfused unit, and an epidemic appears to be developing with significant legal and financial implications.[35] Transfusion of ABO-incompatible blood (1 in 600,000 blood transfusions) is often fatal. Immunomodulation resulting from blood transfusion may manifest as an increased incidence of postoperative infection, increased risk of cancer recurrence and metastases or reactivation of latent viruses.[36] An association was found with transfusion of non-leucodepleted allogeneic blood and postoperative pneumonia in patients after coronary artery bypass graft surgery. This effect increased with increase in storage time of the transfused blood.[37] In a retrospective study over 11 years from 20 hospitals in 9598 patients over 60 years old with hip fractures undergoing hip surgery, a dose-response risk of bacterial infection with transfusion was found even after adjustment for co-morbidities. This resulted in an increase in hospitalisation cost of US$14,000 per patient.[38] Assuming that the immunomodulatory effects are white-cell mediated, a meta-analysis[39] accepted only RCTs or prospective cohort studies with leukocyte-depleted or

TABLE I: SUPRANORMALISATION OF OXYGEN DELIVERY—% MORTALITY

	Control	Protocol
Shoemaker et al[31]	28%	4%
Boyd et al[32]	22.2%	5.7%
Wilson et al[33]	17%	3%

autologous blood controls. With these strict inclusion criteria, the 95% confidence intervals of the summary risk ratios were 0.79 – 1.15 for all-cause mortality, and 0.88 – 1.28 for cancer recurrence. There was heterogeneity in the postoperative infection data, and only 4 RCTs were appropriate for meta-analysis. The 95% confidence interval of the summary risk ratio for postoperative infection was 0.76 – 1.32. The power to detect relative increases of 20% with allogeneic transfusion was 76% for mortality, 76% for cancer recurrence, and 93% for infection. The results suggest that the magnitude of the adverse effects was less than 20%. Conversely, meta-analyses may give results that are discordant with large definitive RCTs.

Unfortunately, transfusion is the simplest way to manipulate haematocrit. However, if the purpose of a red cell transfusion is oxygen consumption, therapeutic efficacy has not been demonstrated in this regard in the critically ill. The red cell membrane undergoes changes in storage that make it more rigid and increases its aggregability. In animal studies, blood transfusion results in trapping of red cells in various organs.[40] In a number of RCTs in ICU patients, transfusion had no effect on VO_2 in patients with cardiac and septic shock,[41] in ARDS patients[42] or in mechanically ventilated septic patients.[43] Splanchnic ischaemia has been reported in patients receiving old red cells. However in critically ill patients, red blood cell deformability is already decreased, and in this situation, red blood cell transfusion may actually improve the red blood cell deformability.[44]

Interpreting red cell transfusion trials is fraught with confounding factors that may influence the results. Utilising an uncontrolled haemorrhagic shock model in rats, a 10-minute delay in blood replacement could exacerbate haemorrhagic shock and increase mortality,[45] despite achieving the same Hct. Furthermore, the effect of transfusion cannot be divorced from the blood pressure achieved during resuscitation. In a similar shock model, mortality was related to the interaction between haemodilution (anaemia) and mean arterial pressure,[46] such that anaemia was not detrimental in hypotensive resuscitation, while in normotensive rats, anaemia resulted in poor outcome. Filtering blood of the leukocytes prior to transfusion appears to lower the risk of postoperative infection.[47] The age of blood transfused also seems to have a correlation with mortality and morbidity.[48]

In a RCT involving 838 patients in 25 ICUs, comparing a restrictive strategy of red cell transfusion (maintaining a Hb level between 70 and 90 $g.L^{-1}$) to a liberal strategy of red cell transfusion (maintaining a Hb level between 100 and 120 $g.L^{-1}$), mortality during hospitalisation was significantly lower in the restrictive-strategy group (22.2% versus 28.1%), though death from all causes in the 30 days after admission to the ICU was not different. In patients with an APACHE II of 20 or less, and for patients under 55 years of age, the 30-day mortality was significantly lower in the restrictive-strategy group. Interestingly, cardiac events, primarily pulmonary oedema and myocardial infarction, were more frequent in the liberal-strategy group during the stay in the ICU. In patients with a diagnosis of cardiac disease (26% of enrolled patients), there was no difference in the 30-day mortality between the groups.[49] A Hct of roughly 21% to 27% may be the optimum Hct in the critically ill where transfusion is concerned.

The optimum Hct by transfusion may not be optimum Hct financially. Direct costs of units are irrelevant, and the complication costs have been variously estimated to be around 10 times higher, with an estimated US$400 to $900 per unit exposure. This takes into account excess length of stay, infections, cirrhosis, liver transplantation costs, cancer recurrence and the legal costs of complications.

Alternatives to Transfusion

Various methods of treating anaemia are shown in Table II. Minimising bleeding and iatrogenic blood loss is an essential but often overlooked step in the prevention of anaemia. Nutritional support, haematinics and minimising VO_2 are all important.

EPO stimulates the maturation of erythroid colony-forming units. Side effects include hypertension and hypertensive crises, cerebral convulsions, "flu-like" signs and symptoms, skin reactions, thromboembolism and iron deficiency. EPO abuse by athletes (for whom the optimum Hct is >50%) led to a ban of its use by the International Ski Federation in 1988 and the International Olympic Committee in 1990. EPO has been shown to be useful in minimising blood transfusions perioperatively in patients going for orthopaedic surgery[50] and also in patients going for cardiac surgery.[51] EPO dose-response relationships appear to be similar in patients regardless of age or gender. A dose of 600 $U.kg^{-1}$ weekly is as efficacious as a 300 $U.kg^{-1}$ daily dose.[52]

Experience with EPO usage in the ICU is increasing. Giving recombinant human EPO subcutaneously, 300 $U.kg^{-1}$ for 5 days, then every other day till ICU

TABLE II: TECHNIQUES FOR MANAGING ANAEMIA

• Stop the bleeding	• Nutritional support
• Thrombopoietin	• Respiratory support
• Erythropoietin	• Maintain vascular volume
• Iron (enteral or parenteral)	• Maximise DO_2, minimise VO_2
• Vitamin C	• Red cell transfusion
• Folic acid	• Blood substitutes
• Vitamin B-12	• Hyperbaric oxygen

DO_2: oxygen delivery, VO_2: oxygen consumption

TABLE III: EFFICACY OF rhEPO IN THE CRITICALLY ILL PATIENT[52]

Outcome	rhEPO	Placebo
Units transfused	166	305 (P <0.002)
% transfused	45%	55%
Hct change	4.8%	1.4% (P <0.001)
Final Hct	35.1%	31.6% (P <0.01)

rhEPO: recombinant human erythropoietin, Hct: haematocrit

discharge, or a total of 6 weeks, was effective in raising Hct and reducing the need for red cell transfusions.[53] No increase in mortality or adverse reactions occurred in this RCT of 160 critically ill patients (Table III).

For patients with congestive heart failure and anaemia (Hb <120 $g.L^{-1}$), a randomised trial studied the effects of EPO and intravenous iron. There were increases in Hb and left ventricular ejection fraction with a decreased decline in glomerular filtration rate. Mean hospitalisations decreased 91.1%, and there was a decreased dose requirement for furosemide.[54]

In ESRD patients given EPO, there were major improvements in myocardial function, skeletal muscle strength, exercise capacity, quality of life, cognitive brain function and angina. Regression of left ventricular hypertrophy occurred at Hct 33% to 36%, but complete normalisation did not occur. This may be due to the anaemia not being fully corrected, postulating that the Hct considered optimum was too low, or that the damage had already been done, suggesting that earlier treatment was needed. In an attempt to differentiate between these hypotheses, a number of trials have attempted "normalisation" of Hct in ESRD patients (Table IV).[55] In the largest trial to report the Normal Hct Cardiac Trial (US), the trial was discontinued due to excess mortality in the high Hct group.[56] However, mortality rates decreased

TABLE IV: NORMALISATION OF HAEMOGLOBIN TRIALS[54]

RCTs	Target Hb	Patients	Interim results
Scandinavian Multicentre Trial	13.5 – 16	416	No differences in safety
Canadian Multicentre Trial	13 – 14	159	Left ventricular dilation prevented
Normal Hct Cardiac Trial	Hct 42%	1,233	Stopped, higher mortality in intervention group
Spanish Quality of Life Study	Hct +5% (39)	134	Improvements in all quality of life parameters

RCTs: randomised controlled trials; Hb: haemoglobin; Hct: haematocrit

TABLE V: BLOOD SUBSTITUTE TRIALS

Product	Type	Clinical trials
DCLHb	Human diaspirin-linked	Trauma
HemoLink	Human O-raffinose poly	Phase III, coronary artery surgery
Hemopure	Bovine Gal poly	Phase III, orthopaedic surgery
Perflubron	Perfluorocarbon	Phase III, general surgical
Polyheme	Human Gal poly	Phase III, aortic aneurysm surgery

DCLHb: diaspirin cross-linked haemoglobin, poly: polymerised, Gal: glutaraldehyde

with increasing Hct in both groups with a 30% decrease in risk of death for each 10% increase in Hct.[57]

Blood substitutes that are in development are cell-free haemoglobin, perfluorocarbon emulsions and liposome-encapsulated Hb (Table V). The potential benefits would include a prolonged shelf life, storage at room temperature, universal compatibility and that the products would have been subject to viral inactivation. The disadvantages could be the interference with biochemical tests and their relatively short time in circulation (24 to 48 hours).[58] In Phase I and II studies, ANH with a polymerised bovine Hb solution to a Hct of 2% did not result in renal or hepatic ultrastructural changes or dysfunction, haemodynamic instability or lactic acidosis.[59] Comparing diaspirin cross-linked Hb with fresh autologous blood, there was improved wound healing, hepatocyte proliferation, and less splanchnic translocation in rats.[60] In most efficacy studies, reduction in transfusion triggers could be attained.[61] Survival has been shown in Sprague-Dawley rats that were exchange-transfused up to an 85% reduction in Hct.[62] However, treatment with diaspirin cross-linked Hb as an adjunct to standard therapy was associated with higher mortality in a randomised controlled trial involving 112 trauma patients. [63]

Finally, hyperbaric oxygen may be used for patients in whom refusal of blood transfusion is non-negotiable. Experimentally, pigs completely exsanguinated and replaced with a volume expander had life sustained by hyperbaric oxygen for 4 days. No measurable effects were detected after months of follow-up.[64]

Conclusion

Oxygen utilisation by cells, the requirement for survival, requires DO_2. Haematocrit exists for the purpose of DO_2. The concept of optimum Hct is properly one of optimum DO_2. In the critically ill, it has not been shown that VO_2 is limited by DO_2, nor that DO_2 is limited by Hct. In addition, if DO_2 is achieved by alternative means like blood substitutes or hyperbaric oxygen, the concept of the optimal haematocrit

is irrelevant. The British Committee for Standards in Haematology acknowledges that there are no recognised guidelines on which to base local procedures for the ordering and administration of blood and the management of transfused patients.[65] Blood transfusion, once the standard of care, is now regarded with more caution. EPO is increasingly used in the ICU, and the development of Hb substitutes is a potentially beneficial method in the management of anaemia. Conversely, improvements in screening techniques and the use of leukocyte-depleted blood may result in making the continued use of blood transfusion a safe and viable option.

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