An evidence-based approach to red blood cell transfusions in asymptotically anaemic patients

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ABSTRACT

INTRODUCTION Surgeons and physicians encounter blood transfusions on a daily basis but a robust evidence-based strategy on indications and timing of transfusion in asymptomatic anaemic patients is yet to be determined. For judicious use of blood products, the risks inherent to packed red blood cells, the patient's co-morbidities and haemoglobin (Hb)/haematocrit levels should be considered. This review critiques and summarises the latest available evidence on the indications for transfusions in healthy and cardiac disease patients as well as the timing of transfusions relative to surgery.

METHODS An electronic literature search of the MEDLINE®, Google Scholar™ and Trip databases was conducted for articles published in English between January 2006 and January 2015. Studies discussing timing and indications of transfusion in medical and surgical patients were retrieved. Bibliographies of studies were checked for other pertinent articles that were missed by the initial search.

FINDINGS Six level 1 studies (randomised controlled trials or systematic reviews) and six professional society guidelines were included in this review. In healthy patients without cardiac disease, a restrictive transfusion trigger of Hb 70–80g/l is safe and appropriate whereas in cardiac patients, the trigger is Hb 80–100g/l. The literature on timing of transfusions relative to surgery is limited. For the studies available, preoperative transfusions were associated with a decreased incidence of subsequent transfusions and timing of transfusions did not affect the rates of colorectal cancer recurrence.

KEYWORDS

Blood transfusion – Transfusion trigger

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In 2012–2013 Canadian Blood Services issued nearly 990,000 units of packed red blood cells (pRBC) across the nation.¹ Blood is a limited resource with risks so transfusion needs more rigorous adherence to best evidence. There are large variations in transfusion practice. This review focuses on asymptomatic anaemic adult patients and does not discuss blood transfusions in paediatric or critically ill patients. Transfusion indications, recommendations, risks and timing relative to surgery are based on current best available evidence, namely consensus guidelines and level 1 studies (systematic reviews and randomised controlled trials [RCTs]). Alternative therapies such as erythropoietin are a large topic that will not be addressed in this review.

Methods

For the purpose of this review, a list was put together of transfusion questions that are relevant in day-to-day practice to medical and surgical patients. The focus was on the indications for transfusion in healthy and cardiac disease patients. This paper is not intended to be an extensive systematic review but a selection of recent key articles that

may guide clinical practice. Only level 1 studies and professional society guidelines were incorporated.

An electronic literature search was performed on MEDLINE®, Trip and Google Scholar™ for articles published in English between January 2006 and January 2015. Key search words were “transfusion triggers”, “transfusion strategies” and “transfusion indications”. The Boolean operator AND combined keywords with “red blood cells”. Titles and abstracts were reviewed first, then bibliographies. Relevant citations were incorporated. Studies that investigated paediatric, critically ill or trauma populations were excluded.

Results

Indications for pRBC transfusion in asymptomatic patients without CAD

Haemoglobin (Hb) is the most common objective parameter on which to base transfusion decisions. Recent transfusion recommendations are summarised in Table 1.^{2–15} A critical appraisal of some studies will be provided to avoid duplication with Table 1. Several studies agree it is appropriate to transfuse when Hb <70g/l.^{4,5,9,11} Conversely, when

Table 1 Summary recent transfusion articles (2006–2014)

Paper	Study design	Results / transfusion trigger
American College of Physicians clinical practice guideline, 2013 ²	Systematic literature review	Hb 70–80g/l: Transfuse in hospitalised patients with CAD
Myocardial Ischemia and Transfusion trial, 2013 ³	Multicentre RCT ($n=110$) Patients: ACS or unstable angina Liberal arm (Hb <100g/l) vs restrictive arm (Hb <80g/l) or any symptoms regardless of Hb level	Hb <100g/l: Transfusion at higher Hb levels associated with lower rates of composite endpoint of death, MI or unscheduled revascularisation within 30 days of randomisation (10.9% vs 25.9%, $p=0.054$ without age adjustment, $p=0.076$ with age adjustment)
Carson (Cochrane review), 2012 ⁴	Systematic review of 19 RCTs ($n=6,264$) with meta-analysis Included studies comparing a liberal vs restrictive transfusion strategy	Hb <70–80g/l: Transfusion probably not essential in patients without CAD or notable bleeding. At time of Cochrane review, no other trials done on patients with CAD so triggers in this subset of patients unknown. Restrictive strategies: <ul style="list-style-type: none"> > Risk of receiving future transfusions decreased by 39% (95% CI: 0.52–0.72) > No increased risk of adverse events (mortality, cardiac events, MI, stroke, pneumonia, VTE) > Decreased hospital mortality (RR: 0.77, 95% CI: 0.62–0.95) > No change to 30-day hospital mortality (RR: 0.85, 95% CI: 0.70–1.03) However, high heterogeneity between trials ($p<0.00001$, $I^2\geq 93\%$)
American Association of Blood Banks, 2012 ⁵	Systematic review of 19 RCTs (using evidence from Cochrane review in 2012)	Hb 70–80g/l: Transfuse in hospitalised stable patients without CAD. High quality evidence, strong recommendation. Hb <80g/l: Transfuse in hospitalised haemodynamically stable patients with pre-existing cardiac disease or symptomatic patients. Moderate quality evidence, weak recommendation. No level specified for ACS patients (paucity of data)
CRIT pilot trial, 2011 ⁶	Multicentre RCT ($n=45$) Patients: acute MI with Hct $\leq 30\%$ Liberal arm (Hct <30%) vs restrictive arm (Hct <24%)	Hct <24%: Lower incidence of composite endpoint of in-hospital death, recurrent MI, or new or worsening congestive heart failure compared with liberal strategy (38% vs 13%, $p=0.046$)
Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair trial, 2011 and 2015 ^{7,8}	Multicentre RCT ($n=2,016$) Patients: cardiovascular disease following hip surgery, age ≥ 50 years Restrictive arm (Hb <80g/l) vs liberal arm (Hb <100g/l)	Hb <80g/l: Not significantly different to transfusing for Hb 100g/l in terms of death at 30 days (4.3% vs 5.2%, ARR: -0.9 percentage points, 99% CI: -1.5–3.4 percentage points), death at 60 days (6.6% vs 7.6%, ARR: -1.0 percentage points, 99% CI: -1.9–4.0 percentage points), in-hospital morbidity (4.3% vs 5.2%, ARR: -0.9 percentage points, 99% CI: -3.3–1.6 percentage points) or independent mobilisation at 60 days (35.2% vs 34.7%, $p=0.90$) Long-term mortality at 3 years did not differ significantly between restrictive arm (409 deaths) and liberal arm (432 deaths); HR: 1.09, 95% CI: 0.95–1.25

Society of Thoracic Surgeons, 2011 ⁹	Combination of literature review, grading of recommendations based on American Heart Association / American College of Cardiology system	Hb <70g/l: Transfusion reasonable Hb 70–100g/l: In CPB patients with critical non-cardiac end organ ischaemia, transfusion not unreasonable. Needs more evidence. Hb >100g/l: Do not transfuse unless critical non-cardiac end organ ischaemia
Transfusion Requirements after Cardiac Surgery trial, 2010 ¹⁰	Single centre RCT (n=50) Patients: elective cardiac surgery Liberal arm (Hct ≤30%) vs restrictive arm (Hb ≤24%)	Hct ≤24%: No difference in composite endpoint of 30-day all-cause mortality and severe morbidity (cardiogenic shock, acute respiratory distress syndrome, or acute renal injury requiring dialysis or haemofiltration) during hospitalisation. Occurrence of endpoint was 10% for liberal arm and 11% for restrictive arm (p=0.85).
Guidelines and Audit Implementation Network, 2009 ¹¹	Combination of literature review and expert panel discussion	Hb <70g/l: For stable patients <65 years with no cardiovascular or cerebrovascular problems Hb <80g/l: For stable patients >65 years with no cardiovascular or cerebrovascular problems Hb <90g/l: For patients with cardiovascular or cerebrovascular history (previous MI, angina, hypertension, heart failure, peripheral vascular disease) Hb <100g/l: For symptomatic patients with anaemia (dyspnoea, angina, palpitations, tachycardia, orthostatic hypotension, syncope) or when active bleeding suspected
European Society of Cardiology, 2007 ¹²	Combination of literature review, expert opinion, panel discussion and open forums	Hb <80g/l or Hct <25%: Transfuse in CAD patients
American Society of Anesthesiologists, 2006 ¹³	Combination of literature review, expert opinion, panel discussion and open forums	Hb <60g/l: Transfuse Hb 60–100g/l: Depends on organ ischaemia, potential or actual ongoing bleeding, patient intravascular status and risk factors for inadequate oxygenation Hb >100g/l: Do not transfuse

ACS = acute coronary syndrome; ARR = absolute risk reduction; CAD = coronary artery disease; CI = confidence interval; CPB = cardiopulmonary bypass; Hb = haemoglobin; Hct = haematocrit; HR = hazard ratio; MI = myocardial infarction; RCT = randomised controlled trial; RR = relative risk; VTE = venous thromboembolism

Hb >100g/l, there is little indication for transfusion.^{9,15} Controversy comes with Hb 70–100g/l.

The American Association of Blood Banks (AABB) recommended Hb 70–80g/l as the target in stable patients without coronary artery disease (CAD).⁵ Their strong recommendations were based on high quality evidence from a systematic review, which pooled 19 RCTs comparing restrictive and liberal transfusion strategies.⁴ A total of 6,000 medical and surgical patients were in the meta-analysis, which found that restrictive strategies decreased future transfusions and in-hospital mortality. There was no difference between risk of adverse events or 30-day mortality. However, a high degree of heterogeneity between trials ($p < 0.00001$, $I^2 \geq 93\%$) and small sample sizes of individual studies (which impact on power to detect clinical differences) call into question the value of this type of 'level 1 evidence'.¹⁴ Overall, these studies recommend Hb 70–80g/l as the transfusion trigger for patients without CAD.

Indications for pRBC transfusions in patients with CAD

Studies are summarised in Table 1. Only critiques of research articles will be discussed to avoid duplication. CAD patients have limited myocardial oxygen delivery and cannot adapt as readily to anaemia.¹⁵ Postoperative morbidity and mortality are significantly higher in patients with ischaemic heart disease than in those without.^{16–18} Raising the Hb level will increase arterial oxygen content and delivery but there is not necessarily a corresponding increase in tissue oxygenation.^{19,20} This may be due to the 'storage lesion' (a series of biochemical changes related to the age of the pRBC). The current shelf life of pRBC is 42 days.²¹ Older pRBC have lower levels of 2,3-diphosphoglycerate, which impairs the ability of Hb to offload oxygen to tissues.²²

Before the 1980s, many clinicians abided by the '10/30 rule': safe surgery required preoperative Hb >10g/dl (100g/l) or haematocrit (Hct) >30%.²³ It is generally accepted

that Hct (%) is roughly three times the Hb value (g/dl).²⁴ This recommendation was originally intended for high risk anaesthesia patients. More restrictive transfusion thresholds have since been adopted.

In 2012 the AABB recommended weakly that hospitalised patients with pre-existing cardiovascular disease be transfused for Hb ≤ 80 g/l or for anaemic symptoms.⁵ There was 'moderate evidence' for this recommendation. For hospitalised haemodynamically stable patients with acute coronary syndrome (ACS), the AABB could not recommend for or against a restrictive transfusion threshold because of 'very low quality (observational) evidence'⁵ and uncontrolled confounding variables.

The 2010 Brazilian Transfusion Requirements After Cardiac Surgery study was a single centre RCT enrolling 50 elective cardiac surgery patients.¹⁰ There was no difference in the composite endpoint of 30-day all-cause mortality, cardiopulmonary morbidity or acute renal injury between patients in the restrictive transfusion group (transfuse for Hct $<24\%$) or those in the liberal group (transfuse for Hct $<30\%$). The authors therefore recommended a restrictive Hct transfusion trigger. Study limitations were that it was a single centre trial not using leucodepleted pRBC. These factors could affect study generalisability as many other institutions use leucodepleted pRBC.

In 2011 Cooper *et al* randomised 45 patients with acute myocardial infarction (AMI) to either a restrictive (Hct $<30\%$) or liberal transfusion protocol (Hct $<24\%$).⁶ Restrictive arm patients had a lower incidence of in-hospital death, recurrent myocardial infarction and congestive heart failure (38% vs 15%, $p=0.046$). This study was not sufficiently powered to detect differences in clinical outcomes. Furthermore, baseline characteristics between treatment arms were not balanced. Several AMI patients underwent revascularisation procedures during the trial, which changes their anaemia tolerance. The trial found that restrictive transfusion offered benefits but its findings will need further validation.

The 2013 Myocardial Ischemia and Transfusion trial showed that restrictive strategies may not be as beneficial as they appear.³ One hundred and ten ACS or unstable angina patients who underwent cardiac catheterisation were randomised to either a liberal transfusion group (Hb <100 g/l) or a restrictive group (Hb <80 g/l). Only 10.9% of patients in the liberal group experienced the composite endpoint of death, myocardial infarction or unscheduled revascularisation 30 days following randomisation, as opposed to 25.9% of restrictive arm patients ($p=0.054$). Age was a confounder (liberal group mean: 67.3 years, restrictive group mean: 74.3 years; $p=0.004$) but after adjusting for this variable, the composite endpoint was still not significantly different between groups ($p=0.076$). Lack of blinding and a small sample size were sources of bias. Overall, these studies recommend Hb ≥ 80 g/l as a transfusion trigger in CAD patients.

Impact of timing of transfusions on surgical outcomes

When is the optimal time to transfuse an anaemic patient in the perioperative period: pre, intra or postoperatively? This

is an area with limited evidence. Preoperative anaemia has been linked to increased risk of 30-day morbidity and mortality in non-cardiac surgery.²⁵ Postoperative anaemia has been associated with impaired surgical recovery²⁶ and delirium.²⁷ To date, there are only two studies directly comparing timing of blood transfusions on surgical outcomes.

An unblinded RCT studied timing of blood transfusions in 60 cardiac surgery patients undergoing cardiopulmonary bypass (CPB).²⁸ Anaemic patients (Hb 100–120g/l) were either given two units of pRBC 1–2 days prior to surgery (treatment group), or transfused intraoperatively or postoperatively (control group). On average, the treatment group received fewer transfusions during CPB (0 vs 2 units), during surgery (0 vs 2 units) and after surgery (2 vs 4 units). Preoperative transfusions reduced intra and postoperative erythrocyte transfusions but did not affect rates of acute kidney injury. Owing to the small sample size, dropout after randomisation and residual confounders, the authors concluded it would be 'inappropriate to modify clinical practice based on the results of this pilot study'.²⁸

Another outcome in the transfusion timing debate is oncological recurrence. A Cochrane review demonstrated that colorectal cancer recurrence rates did not differ between patients who were transfused pre, intra or postoperatively.²⁹ Leucocytes in blood products can cause immunosuppression as well as tumour growth and spread.²⁹ These effects are known as transfusion related immunomodulation and can be mitigated with prestorage leucoreduction. On the other hand, increased transfusions may be an index of more 'nasty' or invasive tumours that cause more severe anaemia preoperatively. A study from 2014 showed that the incidence of anaemia was higher in patients with Dukes' B (65.2%) and Dukes' C (66.6%) colorectal cancer compared with Dukes' A patients (28.5%).³⁰ Larger tumours tend to have more abnormal blood vessels that can bleed.³¹ Furthermore, increased numbers of circulating inflammatory factors such as tumour necrosis factor alpha have been shown to suppress haemoglobin production.³²

Discussion

Doctors are constantly faced with transfusing patients without a well defined evidence-based strategy. A thoughtful risk-benefit assessment that considers the risks of pRBC as well as patient factors must be carried out. This study is a critical analysis of the current transfusion literature on the management of asymptomatic anaemic medical and surgical patients.

An electronic literature search for articles focusing on indications for transfusions (in healthy and cardiac disease patients) and transfusion timing was performed. As with any search strategy, the number and relevance of articles was determined by the keywords and limits set by the user. A wider search was performed with broad terms to avoid missing important papers, at the cost of having more articles to appraise.

The first clinical question was regarding the transfusion of asymptomatic patients without pre-existing CAD. The general consensus was that Hb 70–80g/l is an appropriate

target for transfusion. The second clinical question pertained to asymptomatic CAD patients. All studies agreed that the transfusion trigger should be higher than for healthy patients. Most studies recommended Hb 80g/l^{2,5,7,8,12} to 90g/l¹¹ or Hct 24%^{6,10} to 25%.¹²

Single unit transfusion is controversial. Two recent cardiac surgery studies showed that there is no statistical or clinical difference between one unit of pRBC and two units in terms of acute surgical complications (odds ratio [OR]: 1.112, 95% confidence interval [CI]: 0.59–2.09, $p=0.764$)⁵³ or mortality (OR: 1.44, 95% CI: 0.88–2.35, $p=0.144$).⁵⁴ Generally, one unit of pRBC increases Hb by 10g/l or Hct by 3 percentage points.⁵⁵ Experts recommend transfusing to a target Hb of 70–80g/l in haemodynamically stable medical and surgical patients as well as ambulatory patients. In ACS patients with suspected ischaemia or anaemic symptoms, Hb >100g/l should be maintained.⁵⁶ These recommendations are summarised in Figure 1.

The final clinical question is the timing of transfusion in relation to surgery. There is a paucity of evidence. Patients transfused before cardiac surgery required fewer subsequent

units of blood in comparison to patients transfused intra or postoperatively.²⁸ However, rates of acute kidney injury did not differ between groups. The timing of blood transfusion in colorectal cancer patients did not affect their rates of malignant recurrence.²⁹

Strengths of this review include that it is used the most current available evidence (2006–2015) and incorporated only level 1 studies and professional society guidelines. Limitations pertained to the search strategy itself, as mentioned previously. The clinical question of timing of transfusions is lacking in evidence. The forthcoming Transfusion Indication Threshold Reduction study is a multicentre RCT with 2,000 cardiac surgery patients from 17 UK health centres, comparing a liberal (Hb <90g/l or Hct <27%) versus a restrictive (Hb <75g/l or Hct <22%) transfusion strategy.⁵⁷ The primary outcome is a binary composite endpoint of any serious infectious (sepsis or wound infection) and ischaemic event (stroke, myocardial infarction, gut infarction or acute kidney injury) in the first three months after randomisation. The results may lend more evidence for an appropriate transfusion threshold for CAD patients.

There is wide variation in transfusion practice³⁸ despite evidence that patients have sufficient physiological reserve to tolerate lower transfusion thresholds. Barriers for translation of evidence into practice may be attributed to knowledge, attitude, implementation and reinforcement factors.³⁹ Healthcare providers may not be aware or familiar with clinical practice guidelines. Disagreement with the guidelines or 'clinical inertia' may be attitudinal barriers.⁴⁰ Active implementation/reinforcement strategies consist of educating healthcare workers, implementing evidence-based institutional protocols and auditing adherence. The University of Kentucky Medical Center (UKMC) is one example. In 2010 it adopted a restrictive transfusion protocol by lowering the threshold from Hb 80g/l to 70g/l for select indications. Between 2010 and 2012, UKMC saved 4,492 units of pRBC and over \$943,000; 662 patients avoided transfusion.⁴¹ Physicians who did not adhere to the protocol were contacted to seek justification for transfusion decisions.

Conclusions

Evidence supports that in healthy patients without CAD, a restrictive transfusion threshold of Hb 70–80g/l is safe and appropriate whereas in patients with CAD, the trigger should be higher. Many studies recommend Hb 80g/l or Hct 24–25%. Others prefer a threshold of Hb 90g/l. The evidence regarding timing of transfusions relative to surgery is limited. Preoperative transfusions are associated with fewer transfusions later in the postoperative course and the timing of transfusions does not affect colorectal cancer recurrence rates.

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