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Anaemia and transfusion triggers in critically ill patients – What we have learnt thus far

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Abstract

Anaemia is a common finding in critically ill patients, the cause of which is multi-factorial including: sepsis, haemolysis (and disseminated intravascular coagulation), iatrogenic blood loss secondary to laboratory sampling, post-operative anaemia, bone marrow suppression/failure, decreased production of erythropoietin, anaemia secondary to drugs/toxins, overt or occult blood loss, functional iron deficiency, poor nutrition and haemodilution. Anaemia is associated with deleterious outcomes including increased risk of cardiac-related morbidity and mortality and decrease in oxygen-carrying capacity in the face of increased metabolic demands. There is a growing body of evidence, which demonstrates that packed red blood cell transfusions are associated with poorer outcomes. Clinicians therefore need to weigh the potential benefit of treating anaemia against the desire to avoid unnecessary transfusions. We explored current literature regarding transfusion triggers and morbidity and mortality associated with packed red blood cell transfusions transfusion, concentrating on studies that have been conducted in critical care patients. In addition, we reflected on trials which considered the viability of iron transfusion and erythropoietin in critically unwell patients.

Keywords

Anaemia, critical care, erythropoietin, iron transfusions, transfusion triggers

Introduction

Anaemia is a common finding in critically ill patients, the cause of which is multi-factorial including: sepsis, haemolysis (and disseminated intravascular coagulation), iatrogenic blood loss secondary to laboratory sampling, post-operative anaemia, bone marrow suppression/failure, decreased production of erythropoietin, anaemia secondary to drugs/toxins, overt or occult blood loss, functional iron deficiency, poor nutrition and haemodilution.[1–4]

Anaemia is associated with deleterious outcomes including increased risk of cardiac-related morbidity and mortality and decrease in oxygen-carrying capacity in the face of increased metabolic demands.[5]

There is a growing body of evidence, which demonstrates that packed red blood cell transfusions (PRBC) are associated with poorer outcomes. Clinicians therefore need to weigh the potential benefit of treating anaemia against the desire to avoid unnecessary transfusions.

We explored current literature regarding transfusion triggers and morbidity and mortality associated with PRBC transfusion, concentrating on studies that have been conducted in critical care patients. In addition, we reflected on trials that considered the viability of iron transfusion and erythropoietin in critically unwell patients.

Transfusion triggers and outcomes

Historically, PRBC transfusions were given routinely whenever the haemoglobin concentration fell below 100 g/L, based upon unproven physiological and clinical assumptions.

However, since the multi-centre Transfusion Requirements in Critical Care (TRICC) trial in 1999 in which a broad population of 838 critically ill adults were randomly assigned to either a restrictive transfusion strategy (transfusion threshold of <70 g/L) or a

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liberal transfusion strategy (threshold of <100 g/L),[6] a haemoglobin concentration of <70 g/L became the accepted threshold in most cases.

Mortality in the 30 days after admission to the ICU was lower in the restrictive-strategy group (18.7%) compared to the liberal-strategy group 23.3%, although this result was not significant (95% CI: −0.84% to 10.1%; $p = 0.11$). Overall ICU mortality was also lower (13.9% vs. 16.2%, $p = 0.29$), again not significant.[6]

The results did demonstrate that 30-day mortality was significantly lower in the restrictive-strategy group than in the liberal-strategy group among the patients with an APACHE II score of 20 or less (8.7% vs. 16.1%; $p = 0.03$) and among the patients who were less than 55 years of age (5.7% vs. 13.0%; $p = 0.02$). Furthermore, mortality rates during hospitalisation were statistically lower in the restrictive group (22.2% vs. 28.1%, $p = 0.05$).[6]

The TRISS trial was a multi-centre, partially blinded, randomised trial enrolling 998 patients with septic shock admitted to ICU. Patients were randomised to either a restrictive transfusion regime with transfusion triggers of <70 g/L or a liberal transfusion regime with transfusion triggers of <90 g/L. No statistical difference in 90-day mortality (43% in restrictive group vs. 45% in liberal group; $p = 0.44$), use of organ support defined as the use of vasopressor or inotropic therapy, duration of mechanical ventilation, or renal-replacement therapy at day 28 (16.1% restrictive vs. 19.9% liberal; $p = 0.14$), serious adverse events ($p = 1.0$) or ischaemic events (7.2% restrictive vs. 8.0 liberal group; $p = 0.64$) was found.[7]

Hence, the trial did not show significantly worse or better outcomes when a restrictive regime was used with lower transfusion triggers (compared to the conclusions of the TRICC trial). However, it should be noted that leucodepleted blood was used in this trial, which was not the case in TRICC. Furthermore, the proportion of patients with existing cardiovascular disease represented 14% of the total cohort in this trial whilst they accounted for 20% in the TRICC trial.[7] Pre-existing CVD has been shown to be an independent risk factor mortality in critically unwell patients.[8]

Following the TRICC trial, Vincent et al.[9] investigated the use of PRBC transfusions in critically ill patients and length of ICU stay and mortality, including 4670 patients who were followed up for 28 days or until hospital discharge, inter-institutional transfer or death.

Mortality rates were significantly higher in patients who had been transfused (18.5% vs. 10.1% respectively; $p < 0.01$). Matching patients by degree of organ dysfunction (as measured by the sequential organ failure dysfunction score (SOFA)), those who were transfused had a higher mortality. Transfused patients had higher mortality rates at every admitting haemoglobin level when compared with non-transfused patients. Matching by propensity scores for receipt of a transfusion likewise revealed higher mortality rates in transfused patients. Mean ICU lengths of stay for transfused patients were 7.2 days compared to 2.6 for non-transfused patients.[9]

There were no clear transfusion triggers documented and average pre-transfusion haemoglobin was 84 (±13) g/L, which may confound results.[9]

A similar study by Silvia Junior et al.[8] evaluated the outcomes of 167 critically ill patients admitted to ICU for >72 h under a restrictive transfusion strategy (threshold <70 g/L). Baseline haemoglobin concentration on admission was 106 ± 22 g/L, which reduced to 82 ± 13 g/L by day 28 ($p < 0.001$). Transfusions were administered to 35%. Mortality rates were 61.1% in the transfusion group compared to 48.6% who were not transfused ($p = 0.03$).

Interestingly, when a multivariate statistical analysis was applied, transfusion was a significant independent risk factor for mortality ($p = 0.011$; OR = 2.67; 95% CI: 1.25–5.69). Length of ICU stay and hospital stay were also both longer in the transfusion group: 20 days (3–83) versus 8 days (3–63) ($p < 0{,}001$); and 24 days (3–140) versus 14 days (3–80) ($p = 0.002$), respectively. Furthermore, the group that did not receive transfusions showed a significant improvement in SOFA score on day 28, compared with the baseline SOFA score (6.1 ± 2.9 vs. 4.0 ± 0.8; $p = 0.04$).[8]

The study is limited by the small sample size. Of note, 54% of the subjects enrolled had pre-existing cardiovascular disease and this was also shown to be an independent risk factor for mortality ($p = 0.003$; OR = 6.71).[8]

Marik et al.[10] conducted a systematic review to determine the association between PRBC transfusion, and morbidity and mortality in critical illness. Forty-five studies were identified, which amounted to 272,596 patients (median of 687 patients per study). The outcome measures were mortality, infections, multi-organ dysfunction syndrome and acute respiratory distress syndrome. The overall risks versus benefits of RBC transfusion on patient outcome in each study were classified as risks outweigh benefits, neutral risk or benefits outweigh risks.

In 42 of the 45 studies, the risks of RBC transfusion outweighed the benefits; the risk was neutral in two studies with the benefits outweighing the risks in a subgroup of a single study (elderly patients with an acute myocardial infarction and a haematocrit <30%). Seventeen of 18 studies demonstrated that RBC transfusions were an independent predictor of death (pooled odds ratio (12 studies) 1.7 (95% CI: 1.4–1.9)).[10]

Twenty-two studies examined the association between RBC transfusion and nosocomial infection; in these studies blood transfusion was an independent risk factor. The pooled odds ratio (nine studies) for developing an infectious complication was 1.8 (95%

CI: 1.5–2.2). RBC transfusions similarly increased the risk of developing multi-organ dysfunction syndrome (three studies) and ARDS (six studies). The pooled odds ratio for developing ARDS was 2.5 (95% CI: 1.6–3.3).[10]

More recently, Carson et al.[11] reviewed 30-day mortality and morbidity in participants randomised to restrictive versus liberal PRBC transfusion thresholds. A total of 31 trials, involving 12,587 participants, across a range of clinical specialities met the eligibility criteria. The restrictive transfusion threshold used a lower haemoglobin level to trigger transfusion (most commonly 70 g/L or 80 g/L), and the liberal transfusion threshold used a higher haemoglobin level to trigger transfusion (most commonly 90 g/L to 10 g/L).

Restrictive transfusion strategies reduced the risk of receiving a RBC transfusion by 43% across a broad range of clinical specialties (RR 0.57, 95% CI: 0.49–0.65). Overall, restrictive transfusion did not increase or decrease the risk of 30-day mortality compared with liberal transfusion (RR 0.97, 95% CI: 0.81–1.16) or any of the other outcomes assessed (cardiac events, myocardial infarction, stroke, thromboembolism). Liberal transfusion did not affect the risk of infection (pneumonia, wound, or bacteraemia).[11]

A further systematic review carried out by Holst et al.[12] also compared restrictive versus liberal transfusion strategies. Thirty-one trials totalling 9813 randomised patients were included. The proportion of patients receiving PRBCs and the number of PRBC units transfused (mean difference −1.43, 95% CI: −2.01 to −0.86) were lower with in the restrictive group.

Restrictive compared with liberal transfusions were not associated with risk of death (0.86, 0.74–1.01, 5707 patients, nine lower risk of bias trials), overall morbidity (0.98, 0.85–1.12, 4517 patients, six lower risk of bias trials), or fatal or non-fatal myocardial infarction (1.28, 0.66–2.49, 4730 patients, seven lower risk of bias trials). Results were not affected by the inclusion of trials with unclear or high risk of bias.[12]

Compared with liberal strategies, restrictive transfusion was associated with a reduction in the number of PRBC units and number of patients transfused, but mortality, overall morbidity and myocardial infarction was unaltered.[12]

These two large meta-analyses are limited by inclusion of participants from a broad range of clinical specialities and not necessarily those with critical illness. No subgroup analysis was conducted in critically unwell patients. Therefore, it is questionable to extrapolate these results to critically ill patients.[11,12]

Furthermore, there was inconsistency regarding the transfusion triggers used in the trials ranging between a restrictive trigger of 70–90 g/L in Carson et al. and 70–97 g/L in Holst et al. Trials also varied between the use of both leucocyte depleted and non-leucocyte depleted blood, which may have confounded results.[11,12]

Transfusion in critically ill patients with cardiovascular disease

There are very few studies, which have evaluated transfusion outcomes following a restrictive-transfusion regime versus a liberal transfusion regime in critically unwell patients with either new or pre-existing cardiovascular disease in ICU.

The TRICC trial suggested no significant differences in 30-day mortality in the subgroup of patients with a primary or secondary diagnosis of cardiac disease (20.5% in the restrictive-strategy group vs. 22.9% in the liberal-strategy group (95% CI: −6.7 to 11.3; $p = 0.69$). The authors concluded that this may be due to confounding of results. However, observational studies suggest the prevalence of CVD in ICU patients is around 30% and accounted for only 20% of patients recruited to the TRICC Trial raising the possibility it was underpowered to look for differences in subgroups.[6]

They did report that cardiac events, primarily pulmonary oedema and myocardial infarction were more frequent in the liberal-strategy group than in the restrictive-strategy group during the stay in the ICU (13% vs. 21% respectively, $p < 0.01$).[6]

In the TRISS trial, which concluded no statistical difference in ischaemic events between either group, only 14% of its participants had CVD and the authors also concluded that they had limited power to detect differences in subgroup outcomes, namely ischaemic events.[7]

A meta-analysis carried out by Docherty et al.[13] compared patient outcomes of restrictive versus liberal blood transfusion strategies in patients with cardiovascular disease not undergoing cardiac surgery.

In total, 11 trials enrolling patients with cardiovascular disease ($n = 3033$) were included for meta-analysis (restrictive transfusion, $n = 1514$ patients; liberal transfusion, $n = 1519$). The pooled risk ratio for the association between transfusion thresholds and 30 day mortality was 1.15 (95% CI: 0.88–1.50, $p = 0.50$), with little heterogeneity. The risk of acute coronary syndrome in patients managed with restrictive compared with liberal transfusion was increased (nine trials; RR 1.78, 95% CI: 1.18–2.70, $p = 0.01$).[13]

However, the meta-analysis conducted by Holst et al.[12] concluded that restrictive transfusion strategies were not associated with a relative risk reduction or relative risk increase in fatal or non-fatal myocardial infarction (relative risk 1.28, 95% CI: 0.66–2.49; $p = 0.46$; $I2 = 34\%$). Seven trials assessing fatal or non-fatal myocardial infarction including 4730 patients were defined as trials with lower risk of bias.

Again caution needs to be exercised when translating these results into clinical practice given that the

trials included in both meta-analyses involved both critical and non-critical care patients.

Immunomodulation

Immunomodulation in ICU patients may in part be mediated secondary to transfusion of red cells which in turn maybe detrimental in sepsis.

Taylor et al.[14] collected data from 1711 patients admitted to ICU. Nosocomial infections rates were determined in patients who were transfused compared to those who did not receive a transfusion whilst adjusting for probability of survival by using Mortality Prediction Model (MPM-0).

The mean number of units transfused per patient was 4.0. The nosocomial infection rate for the entire cohort was 5.94%. The nosocomial infection rates for the transfusion group ($n = 416$) and the non-transfusion group ($n = 1301$) were 15.38% and 2.92%, respectively ($p < 0.005$).

A dose-response pattern was identified (the more units of PRBCs transfused, the greater the chance of nosocomial infection; $p < 0.0001$). The transfusion group was six times more likely to develop nosocomial infection compared with the non-transfusion group. Additionally for each unit of packed PRBCs transfused, the odds of developing nosocomial infection were increased by a factor of 1.5.[14]

Allogenic blood transfusion has a profound influence on immunity with cellular and humoral components being adversely affected. A decreased production of interleukin-2 and increased production of prostaglandin-E_2 and TGF-β have been observed following PRBC transfusion, resulting in decreased CD4 helper cells, interleukin-2 receptor-positive helper cells and natural killer cells. Conversely an increase in B cells and CD8 suppressor cells occurs which can further inhibit CD4 cell response and a further immune suppression. Some immune functions return to baseline within hours following PPRBC transfusion, but evidence suggests that long-term or permanent alteration in immune function may occur.[14–17]

Iron transfusions

Whilst haematological indices point towards a syndrome similar to anaemia of chronic disease in ICU patients, absorption of iron is actually stimulated in critical illness and although there may be adequate stores, iron may not be effectively utilised. Release of iron from macrophages in the reticulo-endothelial system is defective, ferritin concentrations are increased, and serum transferrin levels are normal, rather than elevated, resulting in a functional iron deficiency state.[18,19]

Patteril et al.[20] demonstrated that functional iron deficiency was present in 35% of patients at admission to intensive care and was associated with an increased length of stay and duration of SIRS.

A recent meta-analysis examined five RCTs to assess the efficacy and safety of iron supplementation (by any route) compared to placebo/no iron (as control), in anaemic patients in ICU. Primary outcomes were PRBC transfusions and mean haemoglobin concentration. Secondary outcomes included mortality, infection, ICU and hospital length of stay.[21]

Five RCTs recruiting 665 patients met the inclusion criteria; intravenous iron was tested in four of the RCTs. There was no difference in PRBC transfusion requirements (relative risk 0.87, 95% CI: 0.70–1.07, $p = 0.18$, five trials) or mean number of units transfused (MD 0.45, 95% CI: 1.34–0.43, $p = 0.32$, two trials) in patients receiving or not receiving iron.[21]

Subgroup analysis by administration route comparing only IV iron to no iron again confirmed no difference in PRBC transfusion requirements. Similarly, the groups showed no difference in haemoglobin concentration at 10 days or the end of follow up. There was no difference in mortality, in-hospital infection or length of stay.[21]

The results should be interpreted with some caution, however. The population groups had moderate heterogeneity and the majority of the patients included were in surgical ICUs. There was widespread variation in the dosing regimens of iron and methods of administration. The four trials evaluating intravenous iron tested different formulations and dosing schedules. Follow-up time points in all included studies were relatively short – the longest duration was up to 42 days, so any potential long-term clinical benefits of iron therapy may have been missed.[21]

Recently the IRONMAN trial – a multicentre, randomised, placebo-controlled, blinded trial investigated whether early administration of intravenous iron, compared with placebo, reduced PRBC transfusion during hospital stay. Patients admitted to ICU with Hb < 100 g/L were included.[22]

Of the 140 patients enrolled, 70 were assigned to intravenous iron and 70 to placebo. The iron group received 97 PRBC units versus 136 PRBC units in the placebo group, yielding an incidence rate ratio of 0.71 (95% CI: 0.43–1.18, $p = 0.19$), resulting in no statistically significant lowering of PRBC transfusion requirement. Median haemoglobin at hospital discharge was, however, significantly higher in the intravenous iron group than in the placebo group (107 g/L vs. 100 g/L $p = 0.02$]. No significant difference between the groups in length of hospital stay or adverse events was seen.[22]

This study was again limited by heterogeneity of severity of illness and diagnosis, and there was no transfusion trigger set.[22]

Thus, the available evidence suggests that IV iron transfusions do not reduce transfusion requirements in ICU patients in the acute setting and have no impact on length of ICU stay or mortality.

Erythropoietin in ICU

Erythropoietin (EPO) regulates erythrocyte production and the response to EPO may be blunted in the ICU patient.[23,24]

Rogiers et al.[25] measured serial serum concentrations of EPO in 36 critically ill patients, who stayed more than 7 days in the ICU. Eighteen ambulatory patients with iron-deficiency anaemia served as a control group. A significant inverse correlation between serum EPO and haematocrit levels was found in the control patients ($r = -0.81$, $p < 0.001$), but not in the study group ($r = -0.09$, not significant), suggesting that EPO did not rise appropriately in response to anaemia in critical illness.

Elliot et al.[26] also found inappropriately low EPO levels in ICU patients, which persisted for the duration of the critical illness. Inhibition of the EPO gene response elements by cytokines, which are released in sepsis is a postulated mechanism.[27]

Although endogenous EPO levels tend to be low in ICU, response appears to be maintained. Corwin et al.[28] investigated the use of recombinant human EPO (rHuEPO). In a randomised, placebo-controlled trial of 1302 patients, half of them were administered rHuEPO and the other half placebo. rHuEPO was administered on ICU day 3 and continued weekly for patients who remained in the hospital, for a total of three doses. Patients in the ICU on study day 21 received a fourth dose.[28]

Patients receiving rHuEPO were less likely to undergo transfusion (60.4% placebo vs. 50.5% rHuEPO; $p < .001$; OR 0.67; 95% CI: 0.54–0.83) and a 19% reduction in the total units of PRBCs transfused. There was also a reduction in PRBC units transfused per day alive (ratio of transfusion rates, 0.81; 95% CI: 0.79–0.83; $p = 0.04$) and an increase in haemoglobin from baseline to study end was greater in the rHuEPO group (13.2 g/L vs. 9.4 g/L; $p < 0.001$). Nevertheless, no significant difference in mortality, adverse events or length of hospital stay was observed.[28]

A meta-analysis of 673 RCT's by Zarychanski et al.[29] also compared EPO with placebo/no intervention in ICU patients. This showed no significant effect on the overall mortality (OR 0.86; 95% CI: 0.71–1.05, $I^2 = 0\%$), or the length of hospital stay. Erythropoietin, compared with placebo, significantly reduced the odds of a patient receiving at least one transfusion and the mean number of units of blood transfused per patient was decreased by a modest 0.41 units in the erythropoietin group (95% CI: 0.10–0.74, $I^2 = 79.2\%$).

In contradiction, a further prospective, randomised, placebo-controlled trial was also carried out by Corwin et al.[30] A total of 1460 medical, surgical or trauma patients admitted to the ICU were enrolled. Epoetin alfa (40,000 U) or placebo was administered weekly, for a maximum of 3 weeks and patients were followed for 140 days.

Compared with placebo, epoetin alfa therapy did not result in a decrease in either the number of patients who received a PRBC transfusion (RR epoetin alfa group vs. placebo group, 0.95; 95% CI: 0.85–1.06) or the mean number of PRBCs transfused (4.5 vs. 4.3 units, $p = 0.42$). However, the haemoglobin concentration at day 29 increased more in the epoetin alfa group (16 ± 20 g/L vs. 12 ± 18 g/L, $p < 0.001$). There was a tendency toward lower mortality in trauma patients who were given EPO compared to controls.[30]

Of concern is a large meta-analysis undertaken by Mesgarpour et al.[31] (which included 48 studies (34 RCTs; 14 observational) and involved 944,856 participants), which concluded that the administration of erythropoietin stimulating agents is associated with a significant increase in clinically relevant thrombotic vascular events in critically ill patients.

Hence, the evidence is contradictory for the use of EPO. The first RCT by Corwin et al. and the meta-analysis by Zarychanski et al., however, were both carried out prior to widespread adoption of a restrictive transfusion strategy from 2007, possibly resulting in reporting of more favourable outcomes. There are likely complex underlying patho-physiological changes in critical illness with regards to erythropoiesis that are not yet fully understood.

Conclusion

Trials conducted in ICU patients suggest that blood transfusions are independently associated with increased mortality and morbidity, including a direct causal relationship between quantity of transfusion and occurrence of nosocomial infection. Large meta-analyses have failed to reach a definitive conclusion with respect to clinical benefit of restrictive versus liberal transfusion policy. These trials, however, have not been restricted to ICU patients in whom the underlying physiology is altered.

Importantly an absence of harm has been demonstrated with a restrictive policy, which ultimately results in a reduced number of units of RBC transfused. Given that the evidence suggests that transfusion is independently associated with increased morbidity and mortality in ICU patients and liberal transfusion strategies have not been shown to convey any benefit to patients, any strategy that reduces the occurrence of transfusion must be clinically and economically desirable.

With regard to transfusion triggers in patients with pre-existing or new CVD, there are very few trials existing that examine this in critically ill patients as a subgroup. Therefore, there is paucity of evidence to say whether a restrictive or liberal policy is more efficacious, although tending to support a more liberal policy.

Although the overall evidence supports a restrictive transfusion strategy, high-quality trials in ICU patients are needed to further support this practice.

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