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Prevalence of preoperative anaemia in patients having first-time cardiac surgery and its impact on clinical outcome. A retrospective observational study

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Abstract

The prevalence of anaemia is increasing globally. It has a close association with perioperative blood transfusion which, in turn, results in an increased risk of postoperative complications. Undesirable effects are not only limited to short-term, but also have long-term implications. Despite this, many patients undergo cardiac surgery with undiagnosed and untreated anaemia. We designed a retrospective, observational study to estimate the prevalence of anaemia in patients having cardiac surgery in Auckland District Health Board, blood transfusion rates and associated clinical outcome. Two hundred of seven hundred and twelve (28.1%) patients were anaemic. Red blood cell (RBC) transfusion rates were significantly higher in the anaemic group compared to the non-anaemic group (160 (80%) vs. 192 (38%), p-value <0.0001, RR (CI 95%) 2.133 (1.870-2.433)). Transfusion rates for fresh frozen plasma (FFP), cryoprecipitate and platelets were also higher in the anaemic group. Anaemia was significantly associated with the development of new infection (14 (7%) vs. 15 (2.9%), p-value 0.0193, RR (CI 95%) 2.389 (1.175-4.859)), prolonged ventilation time (47.01 hours vs. 23.59 hours, p-value 0.0076) and prolonged intensive care unit (ICU) stay (80.23 hours vs. 50.27, p-value 0.0011). Preoperative anaemia is highly prevalent and showed a clear link with significantly higher transfusion rates and postoperative morbidity. It is vital that a preoperative management plan for the correction of anaemia should be sought to improve patient safety and outcome.

Keywords

anaemia; cardiac surgery; transfusion rate; clinical outcome; mortality; morbidity

Introduction

There is an increasing prevalence of anaemia in the global population, reaching close to 25%.[1] The prevalence of anaemia in patients undergoing cardiac surgery varies between institutions (22-30%),[2] but has been reported to be as high as 54.4%[3] based on the World Health Organisation (WHO)'s definition of anaemia: haemoglobin (Hb) concentration <13 g/dl for men and <12 g/dl for women.[1] Low preoperative red blood cell mass (preoperative anaemia or small body size) is one of the six variables that stand out as important indicators of high risk of postoperative blood transfusion.[4] It is well known that there is a strong association between red blood cell (RBC) transfusion and postoperative complications. Undesirable effects are not only limited to short-term survival, but also impact long-term survival (16% higher long-term morality risk).[5,6]

In addition, preoperative anaemia alone was found to be an important cause of morbidity and mortality in cardiac surgery in several studies.[2,3,7] In a Canadian, multicenter, cohort study, it was reported that anaemia

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patients were 1.8 times more likely to have in-hospital death, stroke or acute kidney injury post-cardiac surgery.[2]

Postoperative anaemia may occur in up to 90% of patients due to the combination of ongoing blood loss and attenuated erythropoiesis persisting for more than a week from a systemic inflammatory response.[4]

Despite this high global prevalence of an important potentially modifiable factor, no on-site data has been collected at this centre. We designed a retrospective, observational study to estimate the prevalence of preoperative anaemia in patients having cardiac surgery in Auckland City Hospital over a period of 12 months and the associated clinical outcome: rate of blood transfusion, mortality, infection, renal failure, length of ventilatory support and the length of ICU stay were studied. This study aims to illustrate the importance of preoperative anaemia and emphasise the requirement of the management of such a condition.

Methods

The study was approved by the Auckland District Health Board (ADHB) Research Review Committee and by Health and Disability Ethics Committees (HDEC).

Inclusion and exclusion criteria

The study population included all consecutive patients of 18 years of age or above who presented for elective and urgent* surgery at a single cardiothoracic surgical centre over a 12-month period (July 2011 – June 2012). Exclusion criteria included:

- Emergency and salvage* surgeries
- Previous cardiothoracic surgeries
- Patients who had an allogenic blood transfusion within 7 days preoperatively

*see definitions

Outcome

The 'exposure' group were patients with anaemia as defined by the WHO (Hb <13 g/dl for men and <12 g/dl for women). Following the estimation of the prevalence of preoperative anaemia, the primary outcome measure was the transfusion requirements of red blood cells, fresh frozen plasma, cryoprecipitate and platelets. Secondary outcome measures were postoperative 30-day mortality from all causes, new infection*, new renal failure*, ventilation time and length of ICU stay.

Data collection

Variables that may affect outcomes were recorded: patient's age, medical comorbidities, preoperative cardiac function, antiplatelet agents and surgical procedures. Surgical procedures were classified as coronary artery bypass graft (CABG) alone, valve-surgery alone, CABG and valve or other. Other operation included a combination of CABG and valve operation, with or without operations on the aorta.

The above variables and other complications that were encountered during the ICU stay were documented prospectively by Cardiothoracic and Vascular Intensive Care Unit (CVICU) clinicians as part of the CVICU database collection. This database was accessed retrospectively. Haemoglobin and blood transfusion data were collected via the local ADHB and national blood bank databases, respectively.

Statistical analysis

Statistical analysis was performed by a local ADHB statistician. Continuous variables were analysed with a two-sided Wilcoxon rank-sum test. Chi-square and Fisher's exact tests were used for discrete variables.

Definitions

- Elective: routine admission for operation
- Urgent: patients who have not been electively admitted for operation, but who require intervention or surgery on the current admission for medical reasons.
- Emergency: operation before the beginning of the next working day after decision to operate
- Salvage: patients requiring cardiopulmonary resuscitation en route to the operating theatre or PRIOR to induction of anaesthesia.
- New infection: Ventilator-associated pneumonia, septicaemia, line sepsis, deep sternal infection (involves muscle and bone, with or without mediastinal involvement).
- New renal failure: at least two of the following
  - Creatinine increased to >200 mmol/L
  - A doubling or greater increase in creatinine over the preoperative value
  - New requirement of dialysis/haemofiltration

Results

A total of 813 patients had undergone cardiac surgery at Auckland City Hospital between July 2011 and June 2012. One hundred and one patients were excluded

Table 1. Characteristics of patients undergoing cardiac surgery.

	Anaemic (n=200)	Non-anaemic (n=512)	p-value
Gender			
Male	134 (67%)	399 (78%)	
Female	66 (33%)	113 (22%)	
BMI			
Male	27.8 (5.44)	28.2 (5.36)	
Female	29.9 (7.23)	29.2 (6.57)	
Pre-op Medical Problem			
Average age	65.69 (12.7)	62.83 (13.8)	
Chronic pulmonary disease	9 (4.5%)	21 (4.1%)	
Diabetes Mellitus	91 (45.5%)	134 (26.2%)	<0.0001
Hypercholesterolaemia	125 (62.5%)	379 (74%)	
Hypertension	151 (75.5%)	342 (66.8%)	
CRF requiring dialysis	23 (11.5%)	3 (0.6%)	<0.0001
LV function			
Good (>50%)	139 (69.5%)	367 (71.7%)	
Moderate (30-50%)	53 (26.5%)	119 (23.2%)	
Poor (<30%)	8 (4%)	26 (5.1%)	
Pre-op medication			
Aspirin	137 (68.5%)	391 (76.4%)	
Clopidogrel	15 (7.5%)	59 (11.5%)	
GpIIbIIIa inhibitors	6 (3%)	1 (0.2%)	
Surgery type			
CABG only	107 (53.5%)	300 (58.6%)	
Valve only	42 (21%)	85 (16.6%)	
CABG + Valve	31 (15.5%)	64 (12.5%)	
Other	20 (10%)	63 (12.3%)	
CPB time (min)	108.6 (54.0)	106.9 (42.0)	

Values are mean (SD) or number of patients (%)
BMI: Body mass index; CPB: Cardiopulmonary bypass; CRF: chronic renal failure; LV: Left ventricular; CABG: coronary artery bypass graft.

from the study (92 patients were either redo cases, emergency or salvage cases, 7 patients did not have preoperative Hb data available and 2 patients were excluded because of preoperative blood transfusion within 7 days of the operation). Of the 712 patients, 200 patients (28.1%) had preoperative anaemia, according to the WHO definition. The mean Hb for the anaemic group was 113.0 g/L vs. 143.6 g/L for the non-anaemic group. Female patients were more likely (36.9%) than male (25.1%) to have preoperative anaemia.

Patient characteristics, preoperative anti-thrombotic agents and performed surgeries are summarized in Table 1. The anaemic group had a higher prevalence of diabetes mellitus (45.5% vs. 26.2%; p-value <0.0001) and chronic renal failure requiring dialysis (11.5% vs. 0.6%; p-value <0.0001) compared to the non-anaemic group. The rest of the patient characteristics and types of surgeries were similar between the two groups.

Transfusion rates for RBC were more than two-fold in the anaemic group compared to the non-anaemic group (p-value <0.0001). Table 2 summarizes the transfusion rates in the anaemic and non-anaemic groups. It was noted that, if female anaemic patients were to undergo primary cardiac surgery, the likelihood for transfusion was close to 100%. In addition, the blood product consumptions (RBC, FFP and platelet) per person were significantly different.

When clinical outcomes were compared, the anaemic group showed higher associations with new infection, ventilation time and length of ICU staytime to that of the non-anaemic group. Table 3 summarizes these results. The odds ratios (OR) were calculated for each of them (Figure 1). It did not show the statistical differences in 30-day mortality and new renal impairment.

Discussion

This study has identified that anaemia, based on the WHO definition, was highly prevalent (28.1%) in the cohort of patients who presented for primary cardiac surgeries in ADHB. Anaemia, not surprisingly, was

Table 2. Blood transfusion rates and blood product consumptions per person.

	Anaemic	Non-anaemic	p-value	RR (95% CI)
	(n=200)	(n=512)		
Average Hb (g/L)	113.0 (11.7)	143.6 (11.5)		
RBC transfusion				
Male	95/134 (71%)	128/399 (32%)	<0.0001	
Female	65/66 (98%)	64/113 (57%)	<0.0001	
Total	160/200 (80%)	192/512 (38%)	<0.0001	2.133 (1.870–2.433)
Any blood product transfusion	160/200 (80%)	237/512 (46%)	<0.0001	1.728 (1.539–1.941)
RBC per person	3.55 (4.21)	1.22 (2.88)	<0.0001	
FFP per person	0.94 (2.47)	0.47 (1.38)	0.0309	
Cryo per person	0.15 (0.69)	0.1 (0.55)	0.3387	
Platelet per person	0.75 (1.36)	0.53 (1.16)	0.0407	

Values are mean (SD) or number of patients (%).
RBC: red blood cell; FFP: fresh frozen plasma; Cryo: cryoprecipitate.
Any blood product includes RBC, FFP, Cryo and platelets.

Table 3. Comparison of clinical outcome between anaemic and non-anaemic groups.

	Anaemic	Non-anaemic	p-value	OR (95% CI)
	(n=200)	(n=512)		
30-day mortality	4 (2%)	5 (1%)	0.2772	2.048 (0.556–7.549)
New infection	14 (7%)	15 (2.9%)	0.0193	2.389 (1.175–4.859)
New renal impairment	9 (4.5%)	11 (2.1%)	0.1262	2.095 (0.881–4.978)
Ventilation time (hr)	47.01 (110.17)	23.59 (52.38)	0.0076	
Length of ICU stay (hr)	80.23 (135.29)	50.27 (71.36)	0.0011	

Values are mean (SD) or number of patients (%).
OR: odds ratio; ICU: intensive care unit.

closely associated with female gender, older age and medical comorbidities, including diabetes mellitus and chronic renal failure requiring dialysis.

Patients with anaemia had more than a two-fold risk of receiving allogenic red blood cell transfusions. In addition, the postoperative development of a new infection was more common in the anaemic group (p-value=0.0193) and postoperative ventilation time (p-value=0.0076) and ICU stay (p-value=0.0011) were significantly prolonged. Differences in 30-day mortality did not reach clinical significance, possibly due to the small number of events. Statistical significance for differences in development of new renal failure were also not met. It is, however, important to note that there was a considerable number of people in the anaemic group who were already on dialysis, hence, these did not meet the criteria for new renal impairment postoperatively.

This study does not identify the cause of the anaemia nor does it reveal the cause of the transfusion. It is clear that the anaemic group had a significantly higher incidence of RBC transfusion, as well as other blood products. It is, however, unclear whether the anaemia was the sole cause of this or if the higher prevalence of medical comorbidities had a role to play. It would be extremely difficult to separate anaemia and medical diseases as they are often interlinked. As shown in Table 1, the anaemic group had a significantly higher number of diabetic and renally impaired patients requiring dialysis. This makes the interpretation of the cause and effect rather difficult. Anaemia is a well-known risk factor for not only allogenic transfusion, but also increased morbidity and mortality after cardiac surgery.[8,9] Although there are strong correlations between anaemia and allogenic transfusion, it is not clear if anaemia resulted in the observed outcome independent of transfusion. With current available evidence, it is difficult to quantify which variable contributed to this outcome and by how much.

Administration of blood products is associated with several adverse effects, including viral and bacterial transmissions and increased postoperative nosocomial infections, which are seven-fold more frequent in transfused versus non-transfused patients.[10] Transfusion-related acute lung injury (TRALI) is estimated to occur in 1 in 1000 to 4000 transfusions of plasma-containing products, especially FFP and platelets.[11] Furthermore,

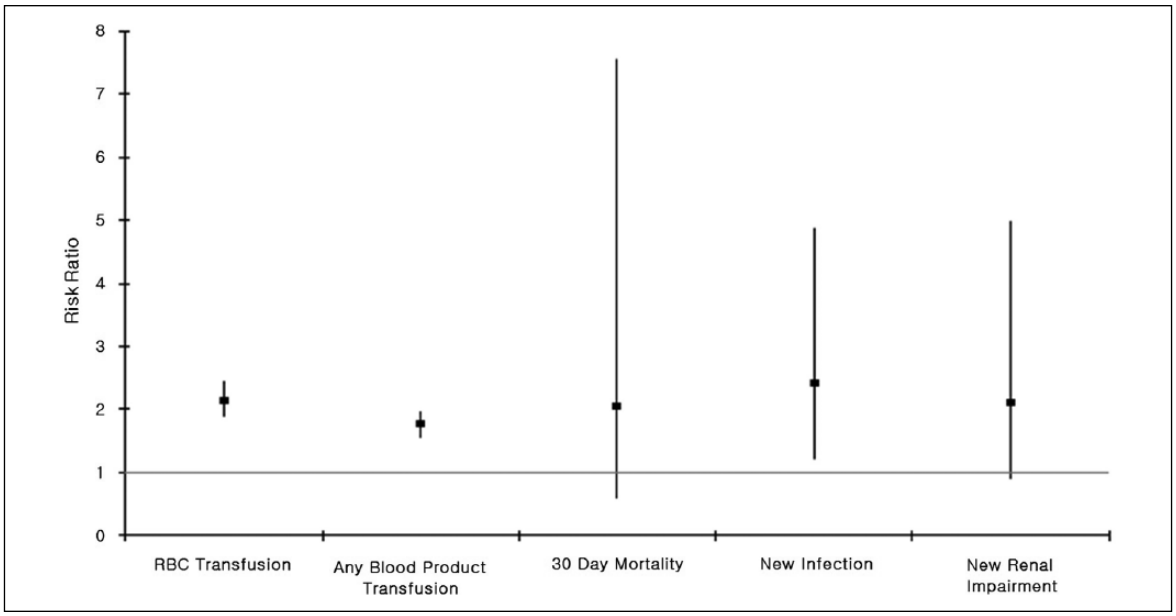

Figure 1. Risk ratio for transfusion and clinical outcomes.

immune suppression and modulation with potential cancer recurrence and risk of multi-organ failure (MOF) is increased with RBC transfusion. Reeves et al. found that there is a dose-response relationship present between transfusion and adverse outcome.[12]

Given the finding above, it seems quite prudent that patient blood management strategies are essential in order to minimise the use of allogenic blood products. This is based on a multidisciplinary, multimodal approach which includes preoperative recognition and management of anaemia, good surgical technique to minimise blood loss intraoperatively, maintenance of normal coagulation profile and restrictive volume management perioperatively. Management should be goal-directed and specific.

In the majority of cases, preoperative anaemia is preventable. Karski et al. found that, following hospital-induced anaemia, iron deficient anaemia (29.3%) was the most common cause of the anaemia in patients presenting for elective cardiac surgery. This was followed by anaemia of chronic renal disease (10.7%), anaemia of chronic disease and folate deficiency.[13] It is a vital priority to investigate and treat anaemia before surgery. More than 85% of the patients having primary cardiac surgeries in ADHB are either elective or urgent, where there are varying degrees of time prior to the surgery, ranging between days and weeks, to investigate and treat the anaemia. Amongst 200 anaemic patients, only 62 (31%) had iron studies done within one month prior to surgery in an attempt to investigate the cause of the anaemia. Of those, at least 26 (42%) had low ferritin levels, suggestive of iron-deficient anaemia.

The management of anaemia should target treating the cause. Because the majority of patients, as stated above, have iron-deficient anaemia and diseases which hinder iron utilisation, it may involve the administration of iron supplements and erythropoiesis-stimulating agents. To date, the quality of available evidence regarding intravenous (IV) iron and recombinant human erythropoietin (rHuEPO) is limited and yet to be tested prospectively in large, randomized, controlled trials. Although its efficacy and safety are not fully established and mainly restricted to a small number of non-cardiac surgical specialties, it is recommended that patients with preoperative anaemia due to iron deficiency have oral or intravenous iron.[14] It is also recommended that patients with serum ferritin levels of <100 ng/ml (or ferritin 100-300 ng/ml and transferring saturation <20%) undergoing a surgical procedure with an expected blood loss of >1500ml may benefit from preoperative iron administration.[15] Intravenous iron may be advantageous in improving rHuEPO response and the rHuEPO dose requirement,[16] but an allergic reaction may be of concern. Perioperative EPO production and iron utilization is reduced as a result of beta-blocker use, the release of cytokines stimulated by the inflammatory response associated with cardiopulmonary bypass and renal ischaemia;[17,18] hence, the administration of EPO may seem logical in patients who are already anaemic preoperatively. The onset of action of EPO usually takes 4 to 6 days and requires the administration of rHuEPO a few days prior, a luxury which is not always available. In European hospitals, an average of only 2.4 days is available between hospital admission and surgery.[18] However, there is evidence that a single dose of rHuEPO

with iron supplement 1 day preoperatively improved postoperative haematocrit and subsequent reduction in allogenic blood transfusion in patients undergoing valvular heart surgeries.[19]

A systematic review by Alghamdi et al., published in 2006, looked at rHuEPO as part of strategies to reduce allogenic blood transfusion.[20] It involved 11 studies with 708 patients (471 patients in the EPO group vs. 237 in the control group). It showed a significant reduction in risk of exposure to allogenic blood transfusion with or without preoperative autologous blood donation; RR = 0.28 (95% CI 0.18-0.44); number needed to treat (NNT) 3 and RR = 0.53 (95% CI 0.32-0.88); NNT 4, respectively.[20] Since then, there have been a number of studies published, looking at the use of rHuEPO with or without supplemental intravenous iron administration prior to cardiac surgeries. Cladellas et. al. conducted a cohort study which involved the administration of rHuEPO for four weeks prior to valvular surgeries.[21] More recently, the focus has shifted more towards the short-term use of rHuEPO due to the time restraint. Weltert et al.[18] and Yoo et al.[19] performed randomized, controlled, blinded studies, involving the short-term (within <3 days prior to the surgery) administration of rHuEPO in off-pump CABG and valvular surgeries, respectively. The above studies consistently showed that the intervention groups had lower RBC transfusion rates, in-hospital morbidity and mortality and higher postoperative haematocrits. It is, however, important to note that the qualities of the studies are limited and the authors suggest the requirement for future, large, robust, randomized, controlled trials.

Safety should be addressed in the use of preoperative rHuEPO. The main complications include hypertension and thromboembolic issues. The thromboembolic complications are associated with an increased haematocrit and those who receive chronic repeated erythropoietin therapy. This is more so if PABD (preoperative autologous blood donation) is not done and the haematocrit is allowed to rise above 50%.[22] D'Ambra et al. reported an increased frequency of mortality, but this was not statistically significant.[23] In addition, studies in patients with chronic heart failure who received the combined IV iron and rHuEPO therapy have shown a better quality of life without increasing the complications associated with it.[24,25] The studies where rHuEPO was used short-term prior to cardiac surgeries in patients with limited haematocrits showed no apparent safety concerns. However, no large-scale safety studies exist in the cardiac cohort and it must be realised that this is "off-label" use. For patients with unstable angina or even stable angina, there is limited support to pursue the use of preoperative EPO because safety data is lacking.[4]

The cost-effectiveness of the active management of preoperative anaemia with iron supplements and rHuEPO would be extremely difficult to estimate. Wetert et al.[18] concluded that short-term rHuEPO administration was not cost-effective when cost was compared against the degree of blood transfusion reduction. One should, however, note that there are hidden costs of complications arising from preoperative anaemia and allogenic blood transfusion, which may significantly override the cost of facilitating rHuEPO and iron administrations. It is recommended that the use of rHuEPO and IV iron should be given to a selected cohort of patient to maximize the clinical benefit and minimise the added cost (e.g. Hb <115 g/dL).[18]

To address the implication of preoperative anaemia, it is important to recognise the degree of the problem and involve clinicians at multiple levels (primary health practitioners, admitting clinicians, surgical and anaesthesia services) for the early detection and management. At the author's institution, the option of preoperative rHuEPO is not being utilised unless medically indicated. However, an algorithm for iron supplements for non-cardiac surgeries has been developed which is available to all clinicians in ADHB and education of its use is being undertaken. Use of such a strategy is to be introduced to our cardiothoracic surgical centre and a future audit of this project will be followed.

In conclusion, this study has demonstrated that preoperative anaemia is highly prevalent and this was associated with significantly high transfusion rates and postoperative morbidity. It is vital that a preoperative management plan for the correction of anaemia should be sought to improve patient clinical outcome.

Declaration of Conflicting Interest

The authors declare that there is no conflict of interest

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