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REPORTS OF ORIGINAL INVESTIGATIONS

Interrelationship of preoperative anemia, intraoperative anemia, and red blood cell transfusion as potentially modifiable risk factors for acute kidney injury in cardiac surgery: a historical multicentre cohort study

Rapports entre l'anémie préopératoire, l'anémie peropératoire et la transfusion de globules rouges vus comme facteurs de risque potentiellement modifiables des lésions rénales aiguës au cours de la chirurgie cardiaque: une étude de cohorte multicentrique historique

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Abstract

Purpose *Acute kidney injury (AKI) is a potentially serious complication of cardiac surgery. Anemia and red blood cell (RBC) transfusion have individually been identified as potentially modifiable risk factors, but their interrelationship with AKI has not been clearly defined. The purpose of this study was to explore the interrelationship of preoperative anemia, intraoperative anemia, and RBC transfusion on the day of surgery with AKI in cardiac surgery.*

Methods *This historical cohort study included 16 hospitals, each contributing data on approximately 100*

Authorship contributions All authors have made substantial contributions to the conception and design of the study and to the acquisition and interpretation of data. *Keyvan Karkouti* conducted the analysis and wrote the first draft of the manuscript. All authors took part in manuscript revision.

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consecutive patients who underwent cardiac surgery with cardiopulmonary bypass. Acute kidney injury was defined as a > 50% increase in creatinine levels during the first postoperative week. Multivariable regression was used to identify the interrelationship between preoperative anemia (hemoglobin < 130 g·L^{-1} in males and < 120 g·L^{-1} in females), intraoperative anemia (hemoglobin < 80 g·L^{-1} during cardiopulmonary bypass), RBC transfusion on the day of surgery, and their interaction terms, after adjusting for site and baseline AKI risk.

Results *Of the 1,444 patients included in the study, 541 (37%) had preoperative anemia, 501 (35%) developed intraoperative anemia, 619 (43%) received RBC transfusions, and 238 (16%) developed AKI. After risk-adjustment, an individual with the combination of these three risk factors had a 2.6-fold (95% confidence interval 2.0 to 3.3) increase in the relative risk of AKI over an individual with none of these risk factors.*

Conclusions *Preoperative anemia, intraoperative anemia, and RBC transfusion on the day of surgery are interrelated risk factors for AKI after cardiac surgery. Targeting these risk factors may reduce the burden of AKI.*

Résumé

Objectif *La lésion rénale aiguë (LRA) est une complication potentiellement grave de la chirurgie cardiaque. L'anémie et la transfusion de globules rouges ont individuellement été identifiées comme étant des facteurs de risque potentiellement modifiables, mais la relation entre ces facteurs et la LRA n'a pas été clairement établie. Le but de cette étude était d'explorer la relation entre l'anémie préopératoire, l'anémie peropératoire et la transfusion de globules rouges le jour de l'intervention avec la LRA en chirurgie cardiaque.*

Méthodes *Cette étude de cohorte historique a inclus 16 hôpitaux, chacun procurant les données d'environ 100 patients consécutifs ayant subi une chirurgie cardiaque avec circulation extracorporelle. La lésion rénale aiguë a été définie par une augmentation du taux de créatinine > 50 % au cours de la première semaine postopératoire. Une analyse en régression multifactorielle a servi à identifier les rapports entre l'anémie préopératoire (hémoglobine < 130 g·L^{-1} chez l'homme et < 120 g·L^{-1} chez la femme), l'anémie peropératoire (hémoglobine < 80 g·L^{-1} pendant la circulation extracorporelle), la transfusion de globules rouges le jour de la chirurgie et leurs interactions, après ajustement pour le site et le risque de base de la LRA.*

Résultats *Sur les 1 444 patients inclus dans l'étude, 541 (37 %) avaient une anémie préopératoire, 501 (35 %) ont développé une anémie peropératoire, 619 (43 %) ont reçu des transfusions de globules rouges et 238 (16 %) ont développé une LRA. Après ajustement pour le risque, la combinaison de ces trois facteurs de risque chez un même individu était associée à une augmentation du risque relatif de la LRA par un facteur de 2,6 (intervalle de confiance à 95 %: 2,0 à 3,3) par rapport à un individu n'ayant aucun de ces facteurs de risque.*

Conclusions *L'anémie préopératoire, l'anémie peropératoire et la transfusion de globules rouges le jour de la chirurgie sont des facteurs de risque inter relié de la LRA après chirurgie cardiaque. La morbidité de la LRA pourrait possiblement être réduite en ciblant ces facteurs de risque.*

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Acute kidney injury (AKI) is a prevalent and prognostically important complication of cardiac surgery, occurring in up to 30% of patients and substantially increasing short- and long-term morbidity and mortality.[1–5] As there are currently no clinically proven therapies that can prevent or treat AKI in cardiac surgery,[1] the best means for reducing the burden of AKI may be through risk factor modification.

Several risk factors for AKI have been identified.[6] While most are not modifiable, anemia and red blood cell (RBC) transfusion have been identified as potentially modifiable risk factors.[2,6] They may therefore be ideal targets for reducing the burden of AKI in cardiac surgery. Importantly, these risk factors are interrelated, and while several studies have explored their individual relationship with AKI, the effect of their interrelationship with AKI has not been clearly defined. Existing evidence suggests that this effect may be synergistic, such that anemic patients may be more susceptible to the deleterious effects of RBC transfusions on the kidney than non-anemic patients.[7–9] This interrelationship, if proven valid, could have important clinical implications for risk management and patient optimization.[10,11] The objective of this study was to explore the interrelationship of preoperative anemia, intraoperative anemia, and RBC transfusion on the day of surgery with AKI in cardiac surgery.

Methods

Study setting, patient sample, and data collection

Seventeen university-affiliated hospitals in Canada, United States, Australia, and New Zealand participated in this retrospective observational study. After obtaining institutional Research Ethics Board approval at the University Health Network (REB 11-0663-AE; initial approval Sept 2011) and at all participating centres, investigators at each hospital retrospectively collected data on 100 consecutive adult (> 18 yr) patients who underwent cardiac surgery with cardiopulmonary bypass (CPB) from January 1, 2010 to December 31, 2011. Cases involving heart transplantation, ventricular assist device placement, or repair of complex congenital abnormalities were excluded because these procedures were not performed at all participating hospitals. Patients were also excluded if they were dialysis-dependent before surgery, had no creatinine or hemoglobin measures before surgery, had no record of timing of perioperative transfusions, or had no creatinine measures after surgery. Based on previous experience,[2] we anticipated that the number of patients obtained from the participating hospitals would include sufficient cases of AKI to allow us to identify the relationships of interest by multivariable analysis.

Using standardized case report forms, detailed perioperative data (including demographics, laboratory tests, medications used, nature of surgery, blood product transfusions on the day of or day after surgery, and major in-hospital postoperative complications) were collected from existing clinical databases and hospital charts. Data were entered into a computerized database with validity checks. All queries were resolved by referring to the patients' original records.

Primary independent variables

The primary variables of interest were preoperative anemia, defined as a hemoglobin concentration < 130 $g{\cdot}L^{-1}$ in males and < 120 $g{\cdot}L^{-1}$ in females,[12] intraoperative anemia, defined as hemoglobin < 80 $g{\cdot}L^{-1}$ during CPB,[8] and RBC transfusion on the day of surgery.

Dependent variable

Patients with a > 50% increase in serum creatinine at any time during the first week after surgery were categorized as having had AKI. This creatinine threshold is consistent with current definitions of AKI.[13]

Statistical analyses

SAS™ version 9.3 (SAS Institute, Inc., Cary, NC, USA) was used for the statistical analyses. Categorical variables were summarized as frequency (percentage) and continuous variables as median [interquartile range] unless otherwise stated. Variability in the incidences of anemia and RBC transfusions across sites was assessed by comparing a logistic regression model, which included each site as a factor, with the null model (intercept only) using a likelihood ratio test.

The unadjusted relationship of preoperative anemia, intraoperative anemia, and RBC transfusion on the day of surgery with AKI was assessed by univariate Poisson regression with robust error variance.[14] Multivariable Poisson regression was used for determining the independent relationships of these three variables as well as their two-way and three-way interaction terms with AKI, after accounting for overdispersion[15] and controlling for the underlying risk of AKI using the Cleveland risk score (Table 1).[16,17] Site was also included as a categorical variable to account for unmeasured case-mix differences. Interaction terms that were not statistically significant ($P > 0.2$) were removed and the model was reconstructed. Seventeen of the 1,444 patients in the study had missing variables and were excluded from these analyses, leaving

Table 1 Cleveland risk score[16] for acute kidney injury

Variable	Score[†]
Female	1
History of congestive heart failure	1
Left ventricular dysfunction	1
Preoperative intra-aortic balloon pump	2
Chronic obstructive pulmonary disease	1
Diabetes	1
Preoperative creatinine 106-186 μmol·L^{-1}	2
Preoperative creatinine > 186 μmol·L^{-1}	5
Redo surgery	1
Emergent surgery	2
Isolated (single) valve surgery	1
Procedures other than isolated CABG or valve surgery	2

[†] Categorize into four classes based on total score: I = 0-2; II = 3-5; III = 6-8; IV = 9-13

CABG = coronary artery bypass graft

1,427 patients. The effect of clustering (within-site correlation) was evaluated by constructing the model with generalized estimating equations.[18]

Bootstrap resampling was used for internal validation. One-thousand computer-generated samples, each including 1,427 patients, were derived from the study cohort by random selection with replacement, and the model was refitted for each sample. The mean and standard deviation bootstrap parameter estimates were used to assess the results of the multivariable modelling.

Results

Data from one site ($n = 100$) could not be used because the timing of the RBC transfusion was not recorded. An additional 139 patients met one or more of the exclusion criteria and were excluded from the analyses, leaving 1,444 patients in the study. Of these, 541 (37%) had preoperative anemia, 501 (35%) developed intraoperative anemia (13 had missing data), 619 (43%) received RBC transfusions on the day of surgery, and 238 (16%) developed AKI (37 of whom required dialysis). There was significant ($P < 0.001$) site variability in the incidences of all four variables (Figure). Sample characteristics are presented in Table 2. In univariable analysis, preoperative anemia, intraoperative anemia, and RBC transfusion on the day of surgery were all significantly associated with AKI, with their respective relative risks (95% confidence interval [CI]) being 1.9 (95% CI 1.5 to 2.3), 2.1 (95% CI 1.7 to 2.6), and 2.0 (95% CI 1.7 to 2.5).

In multivariable analysis, of the interaction terms analyzed, only the interaction of preoperative anemia

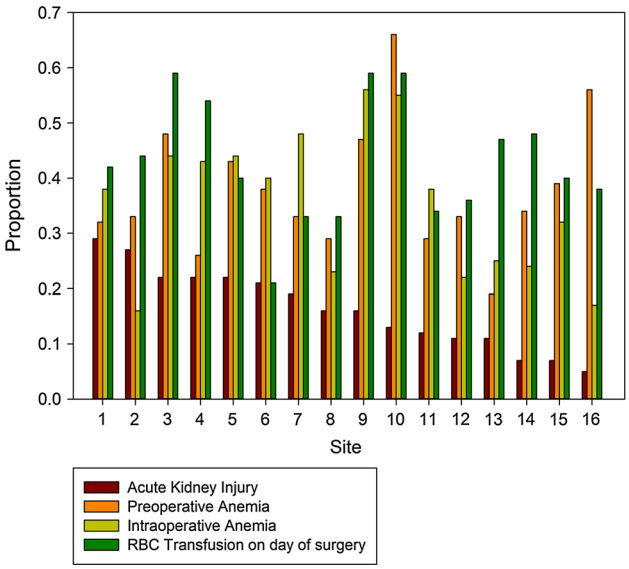

Figure Rates of acute kidney injury, preoperative anemia, intraoperative anemia, and red blood cell (RBC) transfusions on the day of surgery at the participating sites

with RBC transfusion was associated with AKI and hence was retained in the final model (Table 3); the remaining interaction terms had P values > 0.2. With the inclusion of this interaction term, neither preoperative anemia nor RBC transfusion was independently associated with AKI (Tables 3 and 4). In patients with preoperative anemia, however, RBC transfusion was associated with a 1.9-fold (95% CI 1.4 to 2.5) increase in the relative risk of AKI (Table 4). Intraoperative anemia was independently associated with a 1.4-fold (95% CI 1.1 to 1.7) increase in the relative risk of AKI. An individual with the combination of preoperative anemia, intraoperative anemia, and RBC transfusion had a 2.6-fold (95% CI 2.0 to 3.3) increase in the relative risk of AKI over an individual with none of these risk factors (Table 4). The results of bootstrap resampling were consistent with the regression modelling (Table 3).

Discussion

In this retrospective cohort study that included 1,444 patients who underwent cardiac surgery at 16 hospitals, we explored the relationship between preoperative anemia, intraoperative anemia, and RBC transfusion on the day of surgery. We found that more than one-third of patients had one or more of these risk factors and that 16% of patients developed AKI. After accounting for the underlying risk of AKI and the influence of interactions amongst the risk factors, we found that an individual with the combination of preoperative anemia, intraoperative anemia, and RBC

Table 2 Patient demographics and perioperative variables in patients with and without acute kidney injury

Variables	No AKI (n = 1,206)	AKI (n = 238)
Independent variables of primary interest		
Preoperative anemia	415 (34%)	126 (53%)
Intraoperative anemia	379 (32%)	122 (51%)
RBC transfusion (on day of surgery)	473 (39%)	146 (61%)
Cleveland risk score		
Category I	640 (53%)	85 (36%)
Category II	440 (36%)	99 (42%)
Category III	110 (9%)	35 (15%)
Category IV	16 (1%)	19 (8%)
Patient demographics and comorbidities		
Female sex	296 (25%)	74 (31%)
Age (yr)	67 [58-74]	69 [61-77]
Body mass index ($kg \cdot m^{-2}$)	28 [25-32]	29 [25-32]
Diabetes	371 (31%)	91 (38%)
Hypertension	853 (71%)	173 (73%)
Chronic obstructive pulmonary disease	121 (10%)	38 (16%)
Peripheral vascular disease	114 (9%)	29 (12%)
Atrial fibrillation	168 (14%)	41 (17%)
Congestive heart failure	213 (18%)	59 (25%)
Preoperative creatinine ($\mu mol \cdot L^{-1}$)	88 [75-104]	89 [72-115]
Preoperative intra-aortic balloon pump	74 (6%)	31 (13%)
Surgical variables		
Isolated (single) valve surgery	167 (14%)	30 (13%)
Procedures other than isolated CABG or valve surgery	445 (37%)	104 (44%)
Emergent surgery	67 (6%)	23 (10%)
Redo surgery	69 (6%)	22 (9%)
CPB duration (min)	99 [74-130]	116 [87-155]
Circulatory arrest	124 (10%)	33 (14%)

Continuous variables are presented as median [interquartile range], categorical variables as number (percent). CABG = coronary artery bypass graft; RBC = red blood cell; CPB = cardiopulmonary bypass; AKI = acute kidney injury

Table 3 The results of multivariable modelling for the three variables of interest and significant interaction terms

Variable	Poisson Regression		Bootstrap re-sampling
	ß Coefficient (standard error)	P Value	ß Coefficient mean (standard deviation)
Preoperative anemia	−0.03 (0.19)	0.9	−0.05 (0.25)
RBC transfusion	0.14 (0.16)	0.4	0.14 (0.21)
Intraoperative anemia	0.32 (0.12)	0.01	0.33 (0.14)
Preoperative anemia and RBC transfusion interaction term	0.51 (0.23)	0.03	0.53 (0.29)

The model also adjusted for the Cleveland risk score and site. RBC = red blood cell

transfusion had a 2.6-fold (95% CI 2.0 to 3.3) increase in the relative risk of AKI over an individual with none of these risk factors (Table 4).

Anemia and RBC transfusion have been observed in multiple previous studies as important risk factors for AKI after cardiac surgery, but the interrelationship between these variables and AKI has not been as extensively reported.[19,20] In a single-centre observational study comprised of 2,113 propensity-score matched pairs of anemic and non-anemic patients who underwent cardiac surgery with CPB and received up to three units of perioperative RBC transfusions, the risk of AKI was increased in direct proportion to the number of transfusions in both groups, but the increase was much more pronounced in anemic patients.[7] In non-anemic patients, the AKI rate increased from 1.7% in non-transfused patients to 3.2% in those who received three units of RBCs ($P = 0.1$); however, in anemic patients, the rate increased from 1.8% to 6.6% ($P < 0.0001$).[7] In another single-centre observational study by Loor *et al.*, which included 9,144 patients who underwent cardiac surgery with CPB, intraoperative anemia, defined as a nadir hematocrit < 25%, was independently associated with AKI but an RBC transfusion alone was not. As in our study, their reported risk of AKI was highest when both anemia and transfusion were present.[8] The influence of preoperative anemia, however, was not clearly described in their study. Similar findings were reported by Ranucci *et al.* in their study of 1,766 adult patients who underwent isolated coronary artery bypass graft surgery.[9] Overall, therefore, our findings are consistent with the existing single-centre studies described above.

The mechanisms by which perioperative anemia and RBC transfusions may cause AKI in cardiac surgery have not been elucidated. Recent proteomic studies indicate that all patients undergoing cardiac surgery with CPB develop the early stages of ischemia-reperfusion kidney injury, but whether they go on to develop AKI depends on both the occurrence of other renal insults as well as the severity of the ensuing inflammatory response, renal hypoxia, and oxidative stress.[21] Anemia and RBC transfusion could cause AKI either by harming the kidney directly or by increasing patients' susceptibility to concomitant renal insults.

During storage, RBCs undergo several changes that may harm the kidney after transfusion. These changes include a decrease in 2,3-diphosphoglycerate, adenosine triphosphate, and S-nitrosohemoglobin as well as an increase in the concentrations of lactate, potassium, cytokines, iron, and free hemoglobin in the supernatant.[22–26] Red blood cells also

Table 4 Risk-adjusted relative risks (RR) and 95% confidence intervals (CI) of various combinations of preoperative anemia, intraoperative anemia, and red blood cell (RBC) transfusion on the day of surgery for acute kidney injury (AKI)

Combination of Variables of Interest			AKI / *n*	AKI rate	RR	95% CI
Preoperative Anemia	RBC Transfusion	Intraoperative Anemia				
No	No	No	62/586	11%		
Yes	No	No	8/112	7%	1.0	0.7 to 1.4
No	Yes	No	15/132	11%	1.2	0.8 to 1.6
No	No	Yes	9/60	15%	1.4	1.1 to 1.7
Yes	Yes	No	25/96	26%	1.9	1.4 to 2.5
Yes	No	Yes	11/58	19%	1.3	0.9 to 2.0
No	Yes	Yes	24/117	21%	1.6	1.2 to 2.2
Yes	Yes	Yes	78/266	29%	2.6	2.0 to 3.3

Relative risks and confidence intervals derived from the Poisson regression model presented in Table 3 and represent each category's adjusted risk of AKI relative to patients who have none of the risk factors

become progressively less deformable and more fragile during storage in a time-dependent manner. This results in the accumulation of hemoglobin-laden microvesicles in the supernatant as well as predisposing up to 25% of RBCs to early hemolysis within one hour after transfusion.[27–29] Cumulatively, these changes may result in post-transfusion impairment of tissue oxygen delivery and exacerbation of inflammatory response and oxidative stress, thereby harming the kidney.[19] In line with this hypothesis, some (but not all) retrospective studies have found an association between age of blood and adverse outcomes.[30,31]

The contributory effects of anemia to AKI are likely also multifactorial. First, anemic patients (both preoperative and intraoperative) have lower hemoglobin concentrations throughout the perioperative period than non-anemic patients,[32] predisposing them to renal hypoxia.[20] Second, many anemic patients have pre-existing subclinical kidney disease that may increase renal tubular oxygen consumption and oxidative stress,[33–35] thus increasing their susceptibility to concurrent renal insults. Finally, anemic patients have abnormal iron metabolism[36–38] that may affect the clearance of the large amount of iron released when RBCs are hemolyzed, either during storage or soon after transfusion, and this may potentially lead to the presence of free iron and hemoglobin in the circulation.[39,40]

Our study has several limitations. Since neither the cause nor the duration of preoperative anemia were known, it is possible that diseases associated with both anemia and AKI may account for some of the observed relationships. It is also possible that the observed relationships were unduly influenced by other unmeasured confounders such as colloid use.[41] Another limitation is that the number of patients in various categories of anemia and transfusion are small (Table 4), resulting in relatively wide confidence intervals for some of the coefficients (Table 3). Finally, we could not elucidate the cause of anemia, transfusions, or AKI, and we did not have data on the age of the transfused RBCs.[31] Furthermore, we did not use a pre-specified protocol to guide transfusion therapy across all participating sites, and intraoperative management of blood salvage, hemodilution, and the conduct of CPB was left to the individual centres. On the other hand, our study has a number of strengths. Consecutive patients underwent surgery at multiple hospitals; the data used in our study were collected by blinded data abstractors, and the interrelationships between the variables of interest were carefully explored. Nevertheless, further studies are required to confirm or refute our findings.

The natural clinical implication of our findings is that correcting preoperative anemia and avoiding intraoperative anemia and RBC transfusion on the day of surgery could potentially reduce the burden of AKI after cardiac surgery. One relatively simple strategy is to reduce perioperative hemodilution by minimizing fluid administration and using retrograde autologous priming of the cardiopulmonary circuit.[42] Transfusion practice bundles that incorporate point-of-care coagulation testing may also achieve these objectives by reducing blood loss and transfusions through better management of coagulopathy.[43,44] Erythropoietin stimulating agents may also be used to correct preoperative anemia, thereby avoiding intraoperative anemia and RBC transfusion,[42] but the risk-benefit of this intervention in cardiac surgery has not been elucidated.[45]

Other potential options that are currently undergoing evaluation include optimizing oxygen delivery by modifying pump flow;[46] washing of blood to remove the pro-inflammatory molecules, free hemoglobin, and iron that accumulate in the supernatant during storage;[47] haptoglobin therapy to scavenge the free hemoglobin that can be present after CPB and blood transfusion;[48] and prophylactic RBC transfusion one to two days before surgery in patients with preoperative anemia.[49] This latter

approach has been postulated to "reduce the risk of AKI by reducing the severity of anemia, reducing the need for RBC transfusions, allowing time for the transfused blood to recover from the deleterious changes that they undergo during storage, and allowing time for the kidneys to recuperate from the harmful effects of transfused blood before they are exposed to other renal insults" during surgery.[49,50] The risk-benefit profiles of these investigational interventions are yet to be determined.

In conclusion, the results of this multicentre retrospective study showed that preoperative anemia, intraoperative anemia, and RBC transfusion on the day of surgery are interrelated risk factors for AKI after cardiac surgery. Our findings suggest that preventing or correcting these risk factors may therefore reduce the burden of AKI in this setting.

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Conflicts of interest None declared.

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