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ORIGINAL INVESTIGATION

Association between preoperative anemia optimization and major complications after non-cardiac surgery: a retrospective analysis

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Abstract

Background: Anemia is common in the preoperative setting and associated with increased postoperative complications and mortality. However, it is unclear if preoperative anemia optimization reduces postoperative complications. We aimed to assess the association between preoperative anemia optimization and a composite endpoint of major cardiovascular, renal, and pulmonary complications and all-cause mortality within 30 days after noncardiac surgery in adult patients.

Methods: In this retrospective analysis preoperative anemia was defined as hemoglobin concentration below 12.0 $g.dl^{-1}$ in women and 13.0 $g.dl^{-1}$ in men within 6 months before surgery. A propensity score-based generalized estimating equation analysis was used to determine the association between preoperative anemia optimization and the primary outcome. Moreover, mediation analysis was conducted to investigate whether intraoperative red blood cell transfusion or duration of intraoperative hypotension were mediators of the relation between anemia optimization and the primary outcome.

Results: Fifty-seven hundred anemia optimized, and 8721 non-optimized patients met study criteria. The proportion of patients having any component of the composite of major complications and all-cause mortality was 21.5% in the anemia-optimized versus 18.0% in the non-optimized, with confounder-adjusted odds ratio estimate of 0.99 (95% CI 0.86–1.15) for anemia optimization versus non-optimization, p = 0.90. Intraoperative red blood cell transfusion had a minor

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mediation effect on the relationship between preoperative anemia optimization and the primary outcome, whereas duration of intraoperative hypotension was not found to be a mediator.
Conclusion: Preoperative anemia optimization did not appear to be associated with a composite outcome of major in-hospital postoperative cardiovascular, renal, and pulmonary complications and all-cause in-hospital mortality.

Introduction

Preoperative anemia is common in patients undergoing noncardiac surgery, with a prevalence between 5—75% worldwide. It has been associated with postoperative myocardial injury, acute kidney injury, surgical site infections, length of stay[1-3] and 30-day mortality.[4-6] Furthermore, preoperative anemia is associated with allogenic blood transfusion, which is expensive and associated with adverse postoperative outcomes not limited to renal and pulmonary complications, surgical site infection, prolonged hospital stay and increased mortality.[6-9]

Patient blood management services are focused on optimizing patients' hemoglobin and aim to reduce allogenic blood transfusion[10-16] with the goal of reducing postoperative complications. The most common treatable cause of perioperative anemia is iron deficiency, which may result from either acute/chronic blood loss, cancer, nutritional deficiency (which can also cause other hematinic deficiencies such as folate, B12, zinc, copper, etc.), chronic inflammation, or a combination of all these factors.[16-20] Preoperative anemia optimization secondary to iron deficiency aims to replenish iron in the perioperative setting through oral supplementation or intravenous infusion. Recently the U.S. Food and Drug Administration (FDA) has approved the concomitant administration of erythropoietin-stimulating agent for preoperative anemia optimization.[16,19,20] Although, therapy with iron improves preoperative hemoglobin levels, there is controversial evidence about whether preoperative anemia optimization decreases major postoperative complications and mortality.[4,11-15,21-26] Large retrospective studies found that intravenous iron contributes to the reduction of morbidity and mortality, length of stay and nosocomial infections in patients having major procedures.[14,24] However, when preoperative anemia optimization was tested in prospective trials in patients undergoing major elective surgery[22] and abdominal surgeries[15,26,27] and even in metanalysis,[28,29] no difference on postoperative complications, or mortality was found. Therefore, we aimed to assess the association between preoperative anemia optimization and a composite of postoperative complications and all-cause mortality. Specifically, we tested the primary hypothesis that in adult patients with preoperative anemia, anemia optimization is associated with a lower incidence of a composite of major in-hospital cardiovascular, renal, and pulmonary complications and all-cause mortality after noncardiac surgery. Secondarily, we tested whether the association between preoperative anemia optimization and the composite outcome was mediated by either intraoperative red blood cell transfusion or duration of intraoperative hypotension.

Methods

Study population

This retrospective study obtained ethical approval from the Cleveland Clinic by the Institutional Review Board (IRB), Cleveland, Ohio, United States (IRB# 19-201, Executive Director: Bridget Howard) on 21 February 2019, with waived informed consent. The statistical analysis plan was developed a priori and registered with our IRB before data were accessed for analyses.

In this retrospective study, we included adult inpatients who underwent elective noncardiac surgery at 3 Cleveland Clinic hospitals (main campus, Hillcrest and Fairview) from January 2014 until December 2019, and had documented preoperative anemia defined as hemoglobin concentration below 12.0 $g.dl^{-1}$ in women and 13.0 $g.dl^{-1}$ in men within 6 months before surgery (Fig. 1). The eligible surgeries considered in this study included all bowel procedures, all solid organ resections, Whipple procedures, mastectomy with reconstruction, all joint replacements excluding ankle replacement, all multilevel spine procedures, and major vascular procedures (see surgery Current Procedural Terminology [CPT] codes in Supplemental Table 1).

Measurements

The exposure was preoperative anemia optimization according to the Cleveland Clinic Patient blood management protocol. Patient blood management services were implemented at each of the above 3 Cleveland Clinic hospitals during the reported study period, with scrutiny of data at a centralized level. Anemia treatment was indicated by low iron stores, which were defined based on any of the following parameters: ferritin less than 100 $ng.ml^{-1}$ without inflammation; less than 500 $ng.ml^{-1}$ with inflammation and/or transferrin saturation less than 25%. In cases where there was doubt about the absolute iron deficiency, additional testing results suggesting indication for iron replacement included reticulocyte hemoglobin content less than 28 pg or soluble transferrin receptor greater than 5.0 $mg.l^{-1}$. Iron deficit was calculated according to the Ganzoni formula.[30] Iron formulation used was ferric gluconate 125 mg IV daily for 8 doses, up to the day of surgery; or iron sucrose 300 mg IV twice a week for 3 to 4 doses, up to the day of surgery. Other formulations included ferric carboxymaltose 750 mg IV once weekly for 2 doses; however, this was discontinued due to the increased risk of hypophosphatemia, and changed for ferric derisomaltose 1 g IV once, ideally more than a week prior to surgery. Other medications rather than iron supplement intervention used to optimize hemoglobin mainly included folic acid, cyanocobalamin, pyridoxine, leucovorin, darbepoetin alfa, and epoetin alfa.

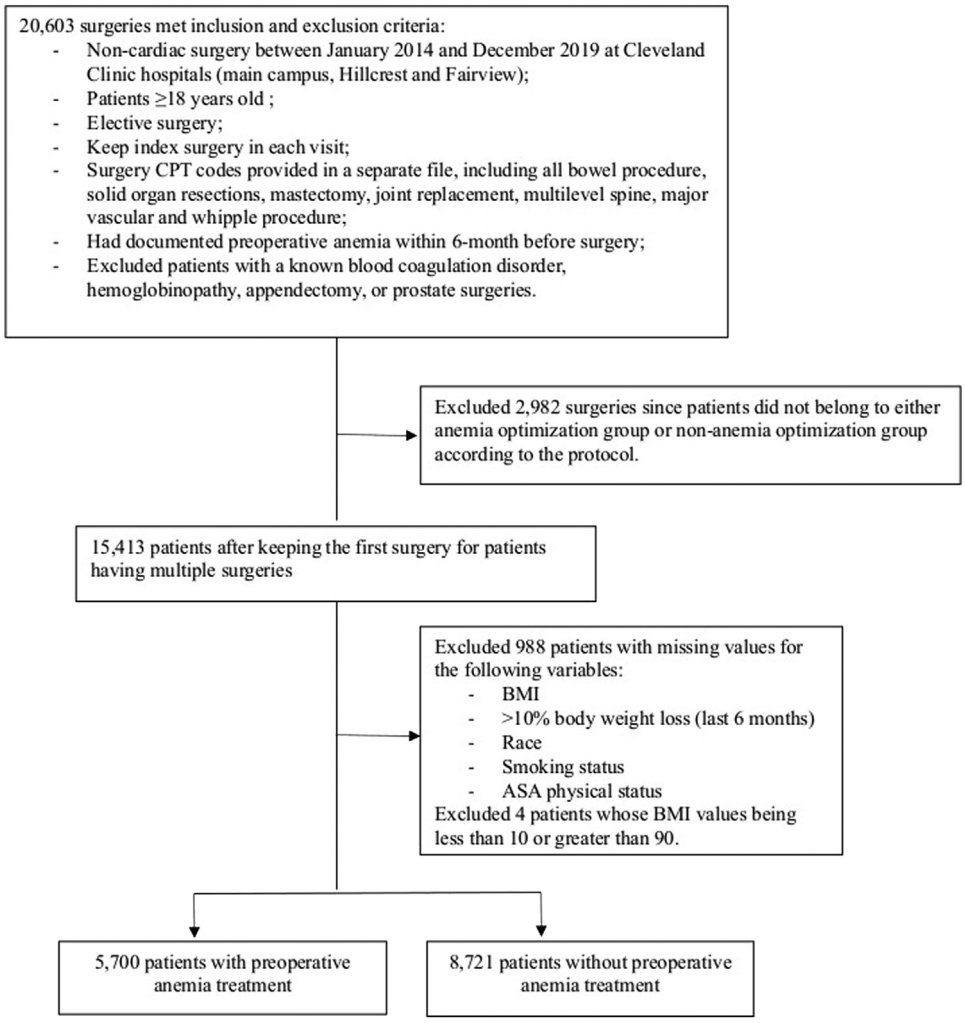

Figure 1 Flow chart of study sample.

Patients who started to take medication for anemia optimization during the 6 months before surgery were included in the anemia optimization group. The non-optimization group consisted of patients who either: 1) Never took any medication for anemia optimization either before or after surgery; 2) Did not have medication for anemia optimization during the 6 months before surgery but may have had it after surgery; or 3) Had previous preoperative anemia treatment but did not have anemia treatment during the 6 months before surgery.

Patient baseline characteristics, surgery data along with intraoperative and postoperative information were obtained from the Cleveland Clinic Perioperative Health Documentation System, Advanced Clinical Guidances (ACG), and Enterprise Data Vault (EDV) databases. Information on patient medication and hemoglobin concentration measurements during anemia optimization period were also extracted from EDV database.

Outcomes

The primary outcome was a composite endpoint of major in-hospital postoperative cardiovascular, renal, and pulmonary complications and all-cause in-hospital mortality. The exploratory outcomes were postoperative in-hospital surgical site infection defined as deep or organ space infection, or sepsis; and Length of Stay (LOS) defined as period from the end of surgery to time of discharge alive. For patients who died in hospital, we assigned the maximum LOS (days) among all patients plus 1 day as their lengths of stay.

Statistical methods

In all analyses we adjusted for the full list of potential confounding variables given in Table 1, including demographic and clinical characteristics such as age, sex, race, body mass index, American Society Anesthesiologists (ASA) physical status, smoking status, and comorbidities (diabetes mellitus, chronic obstructive pulmonary disease, coronary artery disease, etc.). We did this using the method of Inverse Probability of Treatment Weighting (IPTW), a propensity score-based approach.[31,32] A propensity score (p) was first estimated for each patient based on a logistic regression model with the outcome of presurgical anemia optimization (1 = yes, 0 = no) as a function of all potential confounders. Then, IPTW weights defined as 1/p for optimized patients and 1/(1-p) for non-optimized were applied to each patient when comparing the optimization groups on outcomes. Also, balance

Table 1 Patient demographic and clinical characteristics.

Factor	Before IPTW			After IPTW		
	AO (n = 5700)	Non-AO (n = 8721)	ASD	AO (n = 5698)	Non-AO (n = 8724)	ASD
Age (y)	64 ± 15	62 ± 16	0.135	63 ± 16	63 ± 16	0.000
Female sex	3261 (57.2)	4818 (55.2)	0.04	3177 (55.8)	4876 (55.9)	0.003
Race			0.018			0.005
White	4715 (82.7)	7206 (82.6)		4706 (82.6)	7218 (82.7)	
Black	823 (14.4)	1254 (14.4)		827 (14.5)	1253 (14.4)	
Asian	45 (0.8)	83 (1.0)		51 (0.9)	77 (0.9)	
Other	117 (2.1)	178 (2.0)		114 (2.0)	175 (2.0)	
BMI ($kg.m^{-2}$)	28 [24, 33]	28 [24, 33]	0.002	28 [24, 33]	28 [24, 33]	0.003
ASA physical status			0.166			0.001
1	18 (0.3)	41 (0.5)		23 (0.4)	35 (0.4)	
2	826 (14.5)	1691 (19.4)		993 (17.4)	1521 (17.4)	
3	3893 (68.3)	5890 (67.5)		3867 (67.9)	5921 (67.9)	
4	954 (16.7)	1092 (12.5)		809 (14.2)	1234 (14.1)	
5	6 (0.1)	5 (0.1)		5 (0.1)	7 (0.1)	
6	3 (0.1)	2 (0.0)		2 (0.0)	5 (0.1)	
Smoking	536 (9.4)	1103 (12.6)	0.104	645 (11.3)	990 (11.4)	0.001
Alcohol abuse	140 (2.5)	86 (0.99)	0.113	91 (1.6)	142 (1.6)	0.003
Diabetes mellitus	1578 (27.7)	2049 (23.5)	0.096	1431 (25.1)	2192 (25.1)	0.000
COPD	651 (11.4)	910 (10.4)	0.032	624 (10.9)	955 (10.9)	0.000
Coronary artery disease	951 (16.7)	1194 (13.7)	0.083	852 (14.9)	1304 (15.0)	0.000
Chronic kidney disease	494 (8.7)	348 (4.0)	0.193	331 (5.8)	503 (5.8)	0.002
Peripheral vascular disease	469 (8.2)	655 (7.5)	0.027	445 (7.8)	678 (7.8)	0.002
Active malignancy	520 (9.1)	994 (11.4)	0.075	598 (10.5)	919 (10.5)	0.001
Stroke or transient ischemic attack	305 (5.4)	545 (6.2)	0.038	335 (5.9)	513 (5.9)	0.001
Congestive heart failure	691 (12.1)	678 (7.8)	0.146	546 (9.6)	831 (9.5)	0.002
Myocardial infarction	615 (10.8)	535 (6.1)	0.168	456 (8.0)	698 (8.0)	0.000
Hypertension	3686 (64.7)	5180 (59.4)	0.109	3503 (61.5)	5362 (61.5)	0.000
Chronic steroid use	200 (3.5)	217 (2.5)	0.060	167 (2.9)	255 (2.9)	0.000
HIV/Aids	6 (0.1)	11 (0.1)	0.006	6 (0.1)	10 (0.1)	0.002
> 10% body weight loss (last 6-months)	1513 (26.5)	1833 (21.0)	0.130	1316 (23.1)	2012 (23.1)	0.001
Liver disease	271 (4.8)	307 (3.5)	0.062	226 (4.0)	347 (4.0)	0.000
Preoperative dialysis	241 (4.2)	115 (1.3)	0.178	140 (2.5)	208 (2.4)	0.004
Rheumatoid arthritis	464 (8.1)	369 (4.2)	0.163	333 (5.8)	517 (5.9)	0.003
Systemic erythematous Lupus	42 (0.7)	46 (0.5)	0.026	34 (0.6)	53 (0.6)	0.000

Data are reported as mean ± SD, Median [P25, P75], or n (column %).
AO, Preoperative Anemia Optimization; Non-AO, without preoperative Anemia Optimization; IPTW, Inverse Probability of Treatment Weighting, one propensity score method to adjust for confounding; ASA, American Society of Anesthesiologists; BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; AIDS, Acquired Immunodeficiency Syndrome; ASD, Absolute Standardized Difference; roughly, the difference in means or proportions divided by pooled standard deviation; ASD < 0.10 was considered evidence of covariates balance between AO and non-AO groups in this study.

on baseline variables after applying IPTW weights was assessed using the Absolute Standardized Difference (ASD), with ASD < 0.10 considered evidence of sufficient balance.[31] For comparison purposes, ASDs of baseline variables based on raw data were also reported.

For the primary analysis, we assessed the association between preoperative anemia optimization and the composite of major complications and in-hospital all-cause mortality after noncardiac surgery using a Generalized Estimating Equation (GEE) distinct effects model. Specifically, the primary outcome was not analyzed as a collapsed composite of "any versus none", but rather as a vector in which the treatment effect on each component was estimated separately in a single GEE model, adjusting for the within-subject correlation across the components. From this model we estimated the average relative effect odds ratio by averaging the log-odds ratios across the components.[33] We further assessed whether the association between anemia optimization and outcomes was consistent across the components by testing the treatment-by-component interaction in the GEE model. Odds Ratios (OR) for each component were also reported (with Bonferroni correction for 4 components).

We also conducted a post-hoc sensitivity analysis on the association between preoperative anemia optimization and the primary composite outcome including only the anemia-optimized patients who had increased hemoglobin values after optimization and all the non-optimized patients used in our primary analysis. The above-mentioned GEE distinct

effects model estimatng the average relative effect odds ratio was again applied.

In secondary analyses, we assessed mediation. Specifically, we assessed whether either intraoperative red blood cell transfusion or duration of intraoperative hypotension, where the latter was measured by the Time-Weighted Average (TWA) Mean Arterial Pressure (MAP) < 65 mmHg, which is the area under a MAP < 65 mmHg divided by total surgery time, was a potential mediator of the relationship between anemia optimization and our primary composite outcome. We followed the statistical methods outlined in Mascha et al.[34] to claim that a variable is a mediator of the association between exposure and outcome, which required that these two conditions be satisfied: 1) The potential mediator is significantly associated with the exposure variable after controlling for confounding using IPTW; and 2) Association between potential mediator and outcome variable is statistically significant after adjusting for the exposure variable and confounders (here, using IPTW weights). As well, there should be no evidence of interaction between exposure and mediator on the outcome.

In exploratory analyses, again using IPTW to control for confounding, we assessed the association between anemia optimization and in-hospital surgical site infection using logistic regression. To account for the competing risk of death before being discharged alive, for patients who died before discharge we assigned the maximum LOS (day) among all patients plus 1 day as their lengths of stay. We then assessed the association between optimization and LOS using a 2-sample IPTW-weighted *t*-test.

The significance level was 0.05 for all analyses. The significance criteria for secondary and exploratory analyses were not corrected for multiple comparisons. SAS 9.4 statistical software, Cary, NC, was used for statistical analysis.

Results

Fifty-seven hundred anemia optimization and 8721 non-optimization patients met study criteria (Fig. 1). Patient baseline characteristics were well-balanced (ASD < 0.1) after the inverse probability of treatment weighting was applied for (Table 1, Fig. 2).

The median [quartiles] of hemoglobin concentration before optimization for anemia optimized patients was 11.4 [9.7, 12.6] g.dl^{-1} (n = 3956) while those at comparable times for non-optimized patients were unavailable. The median [quartiles] of preoperative hemoglobin concentration measured on the available closest date before surgery was 11.5 [10.3, 12.6] g.dl^{-1} (n = 5686) for anemia optimized patients, and 11.9 [11.0, 12.9] g.dl^{-1} (n = 8683) for non-optimized. For anemia optimized patients, the change in hemoglobin

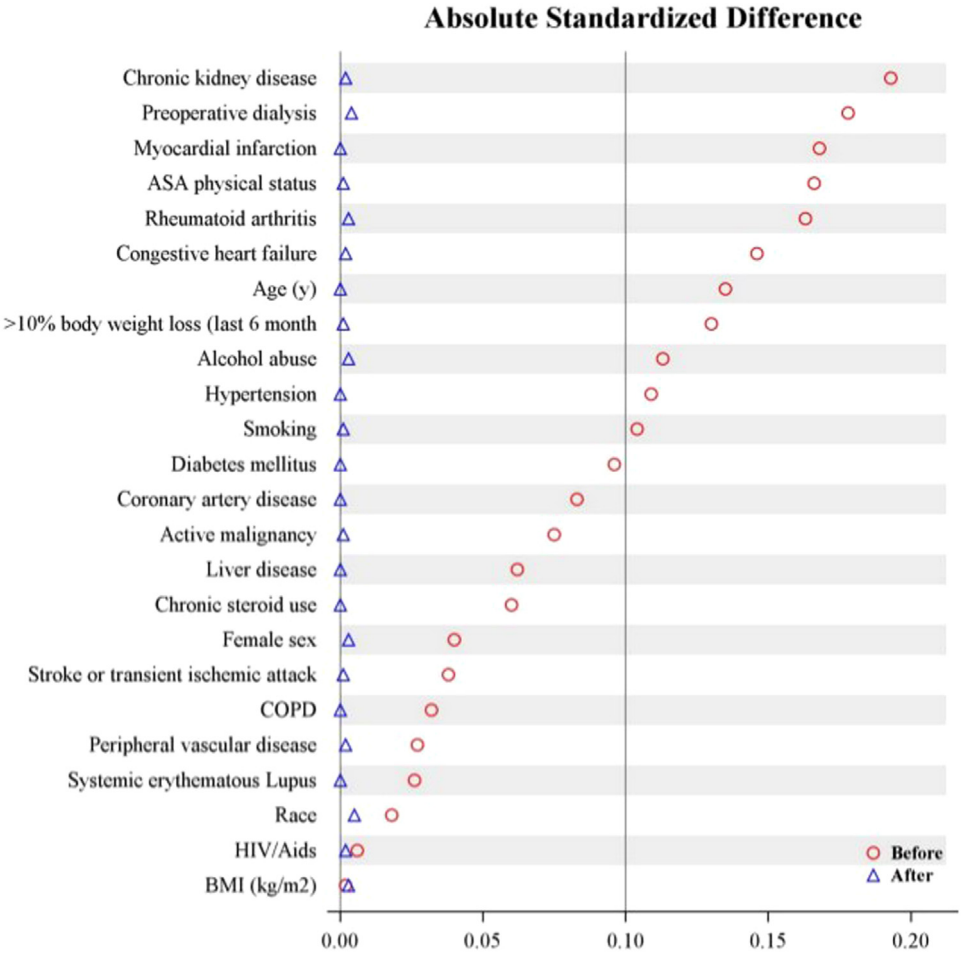

Figure 2 Absolute standardized difference between AO and non-AO groups before and after IPTW.

Table 2 Association between the preoperative anemia optimization and the composite of in-hospital cardiovascular, renal, pulmonary complications, and all-cause in-hospital mortality after surgery (primary analysis and post-hoc sensitivity analysis).

	Incidence		Odds Ratio[a]	
Outcome	AO (n = 5700)	Non-AO (n = 8721)	(CI[b])	*p*-value
Primary analysis				
Overall			**OR (95% CI)[a,b]**	
Average relative effect			0.99 (0.86–1.15)	0.90
Individual component			**OR (98.75% CI)[b]**	
Cardiovascular[c]	278 (4.9)	382 (4.4)	0.93 (0.76–1.15)	0.41
Renal[d]	950 (16.7)	1160 (13.3)	1.05 (0.93–1.19)	0.32
Pulmonary	223 (3.9)	268 (3.1)	1.11 (0.87–1.41)	0.28
All-cause in-hospital mortality	48 (0.84)	50 (0.6)	0.89 (0.51–1.53)	0.58
Collapsed composite	1228 (21.5)	1568 (18.0)		
Post-hoc sensitivity analysis[f]	**AO (n = 1851)**	**Non-AO (n = 8721)**		
Overall			**OR (95% CI)[a,b]**	
Average relative effect			0.81 (0.65–1.03)	0.08
Individual component			**OR (98.75% CI)[b]**	
Cardiovascular[c]	82 (4.4)	382 (4.4)	0.81 (0.59–1.12)	0.10
Renal[d]	322 (17.4)	1160 (13.3)	1.08 (0.90–1.29)	0.30
Pulmonary[e]	68 (3.7)	268 (3.1)	1.01 (0.71–1.45)	0.94
All-cause in-hospital mortality	10 (0.54)	50 (0.57)	0.50 (0.20–1.25)	0.058
Collapsed composite	394 (21.3)	1568 (18.0)		

[a] The average relative effect odds ratio was estimated using a Generalized Estimating Equation (GEE) distinct effects model. The treatment-by-component interaction *p*-value was 0.41 (primary analysis), and 0.06 (post-hoc sensitivity analysis), respectively, suggesting no evidence of heterogeneity in the association across components.

[b] Confidence Interval (CI): *p*-value < 0.05 was considered statistically significant for the average relative effect for the primary composite outcome and presented with 95% CI. The significance criterion for each of four component outcomes was *p*-value < 0.0125, obtained by applying a Bonferroni adjustment (i.e., 0.05/4) to maintain the overall Type I error rate at 5% accounting for multiple testing, and correspondingly, 98.75% CIs were reported.

[c] Defined as any of MINS (myocardial injury after noncardiac surgery), stroke, myocardial infarction, cardiac arrhythmia, congestive heart failure, and venous thromboembolism.

[d] KDIGO stage 1 and above or postoperative new dialysis.

[e] Respiratory failure.

[f] Post-hoc sensitivity analysis including only the anemia-optimized patients who had increased hemoglobin values after optimization and all the non-optimized patients used in our primary analysis.

concentration after anemia optimization, defined as the hemoglobin value measured on the available closest date prior to surgery minus the hemoglobin measured on the closest date before starting anemia optimization treatment, was 0.1 [−0.8, 1.3] $g.dl^{-1}$ (n = 3577), and the time elapsed between these two measured hemoglobin values was 91 [27, 146] days. Among 5700 anemia optimized patients, frequency (%) of patients using different anemia treatment regimens were (1) Intravenous iron only: 811 (14.2); (2) Oral iron only: 2010 (35.3); (3) Both intravenous and oral iron: 397 (7.0); and (4) Other medications: 2482 (43.5), with main other medication (% among 2482 patients) being folic acid (56), cyanocobalamin (45), pyridoxine (7.7), leucovorin (5.6), darbepoetin alfa (3.1), and epoetin alfa (1.6).

A total of 1228/5700 (21.5%) patients under preoperative anemia optimization and 1568/8721 (18.0%) non-optimized patients had at least one component of the composite of major complications and all-cause mortality, with the largest component frequency being renal complications [950/5700 (16.7%) vs. 1160/8721 (13.3%)] (Table 2). Our primary analysis found that preoperative anemia optimization was not associated with the composite outcome, with an estimated average relative effect odds ratio of 0.99 (95% CI 0.86–1.15) for anemia optimization versus non-optimization, p = 0.90. Consistent results were found for each component, with treatment-by-component interaction p = 0.41 and no significant association found for any component (Table 2, Fig. 3).

We also conducted a post-hoc sensitivity analysis on the association between preoperative anemia optimization and the primary composite outcome restricted to anemia optimized patients who had increased hemoglobin values after treatment (n = 1851) and the complete control group (n = 8721). The median [quartiles] hemoglobin change after anemia optimization for anemia optimized patients was 1.3 [0.6, 2.4] $g.dl^{-1}$, n = 1851. The propensity score (and IPTW weight) for each patient was re-calculated in the sensitivity analysis. Again, preoperative anemia optimization was not significantly associated with the primary composite outcome, with estimated average relative effect Odds Ratio (95% CI) of 0.81 (0.65–1.03) for experiencing primary composite outcome in the anemia optimized versus non-optimized patients (Table 2).

Transfusion as mediator

The proportion with intraoperative red blood cell transfusion was 928/5700 (16.3%) in anemia optimization and 1081/

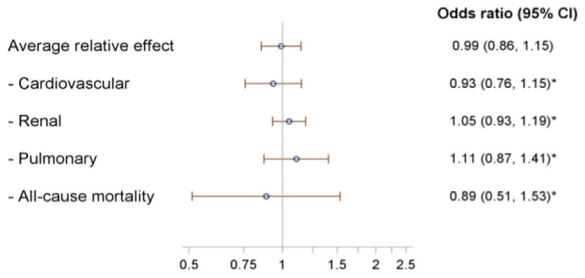

Figure 3 Forest plot of estimated odds ratios for experiencing the primary composite outcome (average relative effect) and for each component outcome for AO patients versus non-AO patients and their CIs based on the GEE model; *denoted 98.75% CI for the odds ratio of experiencing each component outcome. AO, Anemia Optimization; GEE, Generalized Estimating Equation.

8721 (12.4%) in non-optimization patients. The median [quartiles] intraoperative Red Blood Cell (RBC) in transfused patients was 662 [350, 962] ml in anemia optimized and 652 [350, 917] ml in non-optimized patients. Since most patients (86%) did not have intraoperative red blood cell transfusion, we treated it as a binary variable ("Yes" or "No") in the mediation analysis. Anemia optimization was significantly associated with receiving intraoperative RBC transfusion based on an IPTW-based logistic regression model; anemia optimized patients had 1.2 times higher odds of receiving intraoperative RBC transfusion compared to their non-optimized counterparts, with odds ratio (95% CI) of 1.23 (1.1–1.3), $p < 0.0001$. As well, receiving intraoperative RBC transfusion was significantly associated with the primary composite outcome based on the GEE distinct effects model, with estimated average relative effect Odds Ratio (95% CI) of 2.7 (2.2–3.2) for experiencing the primary composite endpoint in patients receiving versus not receiving intraoperative RBC transfusion, $p < 0.0001$ (Supplemental Fig. 1). Finally, the GEE distinct effects model showed no evidence of interaction between anemia optimization and intraoperative RBC transfusion on the primary composite outcome, interaction $p = 0.34$. Therefore, we concluded that intraoperative RBC transfusion was a mediator of the relationship between anemia optimization and the primary composite outcome.

However, this mediation effect appears to be minor because the association between anemia optimization and the composite outcome was virtually identical when we adjusted for the purported mediator of intraoperative RBC transfusion, i.e., the "direct effect", average relative effect OR (95% CI) of 0.98 (0.84–1.15), $p = 0.83$ (Supplemental Fig. 1), versus when we did not, i.e., as in the primary "total effect" analysis with average relative effect OR (95% CI) of 0.99 (0.86–1.15), $p = 0.90$. Similar conclusions held for each component of the composite outcome (Table 2, Supplemental Table 2). As well, since no total effect of anemia optimization on the composite outcome was found, it could be argued that there was very little to mediate in any case.

Duration of intraoperative hypotension as a mediator

The median [quartiles] of estimated overall duration of intraoperative hypotension, measured by the TWA MAP < 65 mmHg was 0.0991 [0, 0.37] mmHg; specifically, 0.0998 [0, 0.39] mmHg in anemia optimized (n = 5689), and 0.0985 [0.0026, 0.36] mmHg in non-optimized patients (n = 8683).

The duration of intraoperative hypotension was significantly associated with the primary composite outcome based on the GEE model, with estimated average relative effect Odds Ratio (95% CI) of 1.02 (1.01–1.03), $p < 0.001$ for having the composite outcome corresponding to 0.1-unit increase of TWA MAP < 65 mmHg. However, the association between anemia optimization and duration of intraoperative hypotension was not significant, with difference in means (95% CI) of duration of intraoperative hypotension in anemia optimization versus non-optimization of 0.021 (−0.0031–0.045) mmHg, $p = 0.09$, using an IPTW-adjusted *t*-test. Therefore, we conclude that duration of intraoperative hypotension was not found to mediate the relationship between anemia optimization and the primary composite outcome.[34]

Exploratory analysis

The percentage with surgical site infection was 63/5700 (1.1%) in anemia optimized versus 104/8721 (1.2%) in non-optimized. In our IPTW-adjusted logistic regression model we did not find an association between anemia optimization status and surgical site infection, with Odds Ratio (95% CI) for having surgical site infection in anemia optimized versus non-optimized being 0.95 (0.69–1.30), $p = 0.75$.

The median [quartiles] of hospital LOS was 4 [3, 7] days for both anemia optimized and non-optimized patients. The IPTW-adjusted *t*-test did not find anemia optimization status to be associated with hospital LOS, with difference of means (95% CI) of LOS in anemia optimized versus non-optimized of −0.13 (−0.69–0.42) day, $p = 0.63$.

Discussion

The results of our study showed that preoperative anemia optimization was not associated with a composite of major in-hospital complications and all-cause mortality after non-cardiac surgery. In our cohort, the lack of association could be related to the overall null improvement in the hemoglobin levels before the surgery for anemia optimized patients since they tended to be sicker than their anemia non-optimized counterparts. Similar to our results, previous study results with iron supplementation have been controversial in achieving increase in hemoglobin before surgery and reducing the number of red cell transfusions.[15,22,27,35] Although, when we restricted the analysis to our 1851 optimized patients who showed a median [quartiles] of 1.3 [0.6, 2.4] g. dl^{-1} increase in the hemoglobin levels before surgery, we did not find any association with the incidence of the composite outcome.

We hypothesize that the poor hemoglobin correction among the patients with preoperative optimization can obey several factors: insufficient time prior to surgery to allow effective hematopoietic response, insufficient iron dosing relative to the degree of iron deficit, concomitant hematinic deficiencies that were not corrected (e.g., folate, vitamin B12, zinc, copper, etc.), presence of underlying bone marrow disorder (e.g., myelodysplastic syndromes), anemia of

chronic disease, etc. This suggests the need for enhancing current preoperative anemia optimization protocols to expand the work-up and substrate correction in the initially unresponsive patients.

Our findings support the results of one of the largest trials in this field. The PREVENTT trial, randomized 478 patients to receive ferric carboxymaltose or placebo 10–42 days before elective major abdominal surgery. The trial did not find any reduction in blood transfusion, nor mortality.[22] In cardiac surgery, another 2 randomized trials demonstrated an increase in the hemoglobin level before surgery with anemia optimization but a lack of effect over the reduction of postoperative complications and 30-day mortality.[36,37]

Contrary to our results, large retrospective cohorts showed an association between preoperative anemia optimization and postoperative nosocomial infections, length of hospital stay and even mortality.[14,24] The differences in the results may be explained by the fact that most of the trials that did not find association were done in colorectal[15,26] and cardiac surgery patients. It is worth remembering that unlike orthopedic patients,[24] the anemia of colorectal and cardiac patients is more progressive and multifactorial with less blood loss during surgery.[38] Another important fact might be the role that red blood cell transfusion and hypotension played on the association between anemia optimization and postoperative outcomes, especially on these retrospective studies where mediation was not analyzed.

Interestingly, patients having anemia optimization preoperatively had 1.2 times higher odds of getting red blood cell transfusion when compared with non-optimized patients (Supplemental Fig. 1). The red blood cell transfusions were independent to any surgical intervention. As expected, red blood cell transfusion was associated with higher odds of having the composite outcome. Therefore, there was some evidence that part of the association between anemia optimization status and the primary composite outcome may go through intraoperative red blood cell transfusion, even though no "total effect" of anemia optimization on the primary composite outcome was found. The fact that anemia-optimized patients were more likely to receive RBCs may at least partly explain why there was no reduction in postoperative complications in the anemia optimized versus the non-optimized.

Notably, intraoperative hypotension duration was not found to be a mediator of the association between the anemia optimization status and the composite outcome. Although hypotension duration was significantly associated with the composite of major postoperative complications and all-cause mortality, it was not associated with the anemia optimization status. Currently, the relationship between duration of intraoperative hypotension < 65 mmHg and postoperative complications is well established in observational studies, including for acute kidney injury, myocardial injury, and mortality.[39]

The main limitation is the retrospective nature of the study. There was a strong risk for selection bias and residual and unknown confounders, even though we had a very good balance between groups on all variables after IPTW. Moreover, it was difficult to identify the control group and to decide the period to take between inclusion and surgery. Although sensitivity analysis showed no association, the timing of the treatment group could not be calculated due to external factors. In addition to this, preoperative hemoglobin was not available for some of the control patients, and hemoglobin levels could have decreased or increased during the 6 months before surgery. Moreover, the lack of association could be related to the overall null improvement in the hemoglobin levels before surgery. It is worth mentioning that the outcomes were from Electronic Medical Records where information can be misplaced or lost easily, although, this should not be a bias towards the group.

In summary, anemia optimization was not associated with decrease in risk of major postoperative complications and all-cause mortality. Prospective studies are needed to determine how preoperative anemia optimization needs to be done to have substantial increase in hemoglobin levels to be able to evaluate major postoperative outcomes in future trials.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2023.11.004.

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