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Association between postoperative haemoglobin and myocardial injury after noncardiac surgery: a retrospective cohort analysis

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Abstract

Background: Myocardial injury after noncardiac surgery (MINS) is common, mostly silent, and a strong predictor of postoperative mortality. MINS appears to result from myocardial supply–demand mismatch. Recent data support restrictive perioperative transfusion strategies that can result in low postoperative haemoglobin concentrations. Whether low postoperative haemoglobin is associated with myocardial injury remains unknown. We therefore tested the hypothesis that anaemia is associated with an increased risk of myocardial injury in adults having noncardiac surgery.

Methods: We conducted a retrospective analysis of adults ≥45 yr old who had routine postoperative troponin T (TnT) monitoring after noncardiac surgery at the Cleverland Clinic (including those enrolled in the PeriOperative ISchemic Evaluation-2 Trial [POISE-2], the Safety of Addition of Nitrous Oxide to General Anaesthesia in At-risk Patients Having Major Non-cardiac Surgery [ENIGMA-II], Vascular Events In Noncardiac Surgery Patients Cohort Evaluation Study [VISION], and Anaesthetic Depth and Complications After Major Surgery [BALANCED] trial). Patients with baseline increase in TnT and non-ischaemic aetiologies for TnT increase were excluded. The association between postoperative haemoglobin concentration during the 3 initial postoperative days and the incidence of MINS (fourth-generation TnT ≥0.03 ng ml^{-1} judged as attributable to ischaemia) was assessed using a time-varying covariate Cox proportional hazards survival analysis.

Results: Among 6141 patients, 4480 were analysed. The incidence of MINS was 155/4480 (3.5%), ranging from 0/345 (0%) among patients whose lowest postoperative haemoglobin exceeded 13 g dl^{-1} to 52/611 (8.5%) in patients whose minimum postoperative haemoglobin was <8 g dl^{-1}. The confounder-adjusted hazard ratio [95% confidence interval] for having MINS was 1.29 [1.16–1.42] for every 1 g dl^{-1} decrease in postoperative haemoglobin in a time-varying covariate analysis. Similar associations were identified in sensitivity analyses.

Conclusion: Lower postoperative haemoglobin values are associated with MINS. Whether this association is modifiable by prevention or treatment of anaemia remains to be determined.

Keywords: anaesthesia; cardiovascular risk; noncardiac surgery; perioperative anaemia; postoperative outcomes

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Editor's key points

- Whether low postoperative haemoglobin increases the risk for myocardial injury after noncardiac surgery remains unclear.
- The authors tested the hypothesis that anaemia is associated with increased risk of myocardial injury.
- The authors analysed data from adults who were enrolled in studies that featured routine postoperative troponin monitoring after noncardiac surgery (including POISE-2, ENIGMA-II, VISION, and BALANCED).
- Lower postoperative haemoglobin values were associated with higher risk for MINS.
- The retrospective design cannot determine whether the risk for MINS is modifiable by prevention of or treatment of anaemia.

Myocardial injury after noncardiac surgery (MINS) is defined as troponin elevation within 30 days after noncardiac surgery, judged as a consequence of myocardial ischaemia (i.e. no evidence of a non-ischaemic aetiology, e.g. sepsis and acute atrial fibrillation).[1,2] One of the strongest predictors of mortality after noncardiac surgery is elevated troponin T (TnT) concentrations.[1] In more than 90% of patients, troponin elevations are not accompanied by symptoms, and only about 20–40% have an ischaemic feature (e.g. ischaemic symptoms, electrocardiography abnormalities) satisfying the 4th Universal Definition of Myocardial Infarction criteria; nonetheless, mortality is nearly as high in patients who do not have symptoms as in those who do.[2,3] MINS is largely restricted to patients who have pre-existing coronary artery disease and appears to result from myocardial supply–demand mismatch or thrombus.[4]

Preoperative anaemia is associated with morbidity and mortality in patients having noncardiac surgery.[3,5–7] The WHO defines anaemia as haemoglobin concentrations less than 13 g dl^{-1} in men and less than 12 g dl^{-1} in women. Although this definition applies to general public health, it is possible that different thresholds are appropriate during the perioperative period.[8] Allogeneic blood transfusion is expensive and potentially harmful. Transfusions are associated with surgical site infections, pulmonary complications, sepsis, thromboembolic events, and mortality.[9,10] Consequently, current perioperative guidelines recommend avoiding blood transfusions until haemoglobin reaches 7–8 g dl^{-1} in clinically stable patients because of the lack of trial data demonstrating benefit to those at higher thresholds.[9–13] Low haemoglobin transfusion thresholds may nonetheless be harmful in individuals less capable of tolerating anaemia, such as older individuals, patients with cardiovascular disease or cancer, or those given beta-blockers.[14–17]

Postoperative anaemia is common because of surgical bleeding, haemodilution by intravenous fluids, and baseline conditions. However, it remains unclear whether postoperative anaemia is associated with myocardial injury. We therefore tested the primary hypothesis that low postoperative haemoglobin concentrations during the initial 72 h after surgery are associated with increased risk of MINS in adults ≥45 yr of age having noncardiac surgery. Secondarily, we tested the hypothesis that the preoperative-to-postoperative reduction in haemoglobin concentration is associated with MINS.

Methods

Study population

This multicentre retrospective cohort study was approved by the Cleveland Clinic Institutional Review Board with waived individual consent. The statistical analysis plan was similarly developed and approved before data analysis began, including all pre-defined sensitivity analyses. The study population was from the Cleveland Clinic database and four trials. For the database patients, we included adults ≥45 yr old who had colorectal surgery at the Cleveland Clinic between 2015 and 2018 and had routine (rather than for-cause) postoperative fourth-generation TnT measurements. Troponin was also routinely evaluated in patients who participated in one of four clinical studies: PeriOperative ISchemic Evaluation-2 Trial (POISE-2),[18,19] addition of nitrous oxide to general anaesthesia in at-risk patients having major noncardiac surgery (ENIGMA II),[20] Vascular Events In Noncardiac Surgery Patients Cohort Evaluation Study (VISION),[2] and the Anaesthetic Depth and Complications After Major Surgery (BALANCED) trial.[21] We therefore also included patients from these four trials in our study population.

Inclusion and exclusion criteria

Our primary analysis was restricted to patients who had at least one blood haemoglobin concentration obtained during the initial 3 postoperative days. We excluded patients who had preoperative TnT concentrations >0.03 ng ml^{-1}, patients with TnT elevation potentially from noncardiac origin (Supplementary Table S1), and patients with missing baseline and surgical information. For the secondary analysis that evaluated haemoglobin reduction from baseline, we excluded patients who had no preoperative haemoglobin measurement during the 30 days preceding surgery. We assumed preoperative haemoglobin measures and potential confounding variables were missing at random. All primary and secondary analyses only included participants for whom we had no missing data (complete case analysis).

Exposure of interest

The exposure of interest was the lowest daily haemoglobin measurement documented during the initial 3 postoperative days. For the secondary analysis, we used the difference between the most recent preoperative haemoglobin concentration within the 30 days preceding surgery and the daily haemoglobin concentrations recorded during the initial 3 postoperative days.

Data collection

Demographic, morphometric, baseline laboratory test results, medications and comorbidities, and postoperative data were collected from Cleveland Clinic's electronic medical records system. Intraoperative data were retrieved from the electronic perioperative health documentation system (PHDS). The red blood cell (RBC) transfusion variable included both intraoperative and postoperative transfusions given before the relevant troponin increase.

Primary outcome

The binary primary outcome MINS was defined as at least one fourth-generation TnT plasma concentration measurement

Table 1 Patient demographic, medical, anaesthetic, and surgical characteristics by minimum haemoglobin during the initial 3 postoperative days, N=4480 noncardiac surgeries. Summary statistics presented as N (%) of patients, mean (standard deviation), or median [Q1, Q3] for factors, symmetric continuous variables, and skewed continuous variables, respectively. ACE, angiotensin-converting enzyme; AUC, area under the curve; eGFR, estimated glomerular filtration rate; RBC, red blood cells.

Factor	Minimum postoperative haemoglobin during the initial 3 postoperative days			
	<8 g dl^{-1}	8–11 g dl^{-1}	11–13 g dl^{-1}	>13 g d^{-1}
	N=611 (14%)	N=2237 (49%)	N=1287 (29%)	N=345 (8%)
Haemoglobin, g dl^{-1}	7.3 [6.8, 7.6]	9.6 [8.9, 10.3]	11.8 [11.4, 12.3]	13.5 [13.2, 14.0]
Patient characteristics				
Age, yr	63 (10)	63 (10)	62 (9.5)	61 (8.5)
Sex				
Female	373 (61)	1257 (56)	518 (40)	41 (12)
Male	238 (39)	980 (44)	769 (60)	304 (88)
BMI	28 (7)	29 (8)	29 (7)	30 (6)
Race				
Caucasian	525 (86)	1956 (87)	1165 (90)	315 (91)
African American	60 (10)	197 (9)	76 (6)	21 (6.1)
Other	26 (4)	84 (4)	46 (4)	9 (2.6)
Smoking status				
Current smoker	84 (14)	273 (12)	178 (14)	65 (19)
Past smoker	259 (42)	949 (42)	531 (41)	138 (40)
Never smoker	268 (44)	1015 (46)	578 (45)	142 (41)
Baseline characteristics				
Preoperative haemoglobin, g dl^{-1}	12 [10,13]	13 [12,14]	14 [13,15]	15 [15,16]
Female	12 [10, 13]	13 [12, 14]	14 [13, 14]	15 [14, 15]
Male	12 [10, 14]	13 [12, 14]	14 [14, 15]	15 [15, 16]
Creatinine, mg dl^{-1}	0.8 (0.2)	0.8 (0.2)	0.9 (0.2)	0.9 (0.2)
Preoperative eGFR, ml min 1.73 m^2	86 [74, 97]	84 [73, 95]	85 [74, 95]	85 [74, 95]
Medication use				
Beta blockers	18 (2.9)	52 (2.3)	22 (1.7)	4 (1.2)
ACE inhibitors	2 (0.3)	24 (1.1)	11 (0.9)	5 (1.4)
Statins	13 (2.1)	41 (1.8)	25 (1.9)	4 (1.2)
Steroids	19 (3.1)	58 (2.6)	31 (2.4)	3 (0.9)
Aspirin	5 (0.8)	29 (1.3)	14 (1.1)	3 (0.9)
Anti-aggregants	2 (0.3)	3 (0.1)	4 (0.3)	0 (0.0)
Oral anticoagulants	2 (0.3)	9 (0.4)	3 (0.2)	1 (0.3)
Comorbidities				
Cardiac disease	223 (37)	679 (30)	327 (25)	85 (25)
Pulmonary disease	114 (19)	372 (17)	189 (15)	32 (9)
Renal failure	25 (4)	37 (2)	16 (1)	1 (0.3)
Metastatic cancer	74 (12)	205 (9)	84 (7)	10 (3)
Solid tumour without metastasis	131 (21)	539 (24)	335 (26)	81 (24)
Liver disease	34 (6)	86 (4)	44 (3)	12 (4)
Haemato-lymphatic cancer	10 (2)	40 (2)	14 (1)	4 (1)
Surgical anaesthetic variables				
Year of surgery				
2010	6 (1.0)	25 (1.1)	6 (0.47)	1 (0.29)
2011	21 (3.4)	131 (5.9)	56 (4.4)	18 (5.2)
2012	100 (16)	370 (17)	191 (15)	41 (12)
2013	74 (12)	300 (13)	133 (10)	34 (10)
2014	14 (2.3)	36 (1.6)	23 (1.8)	2 (0.6)
2015	83 (14)	320 (14)	217 (17)	53 (15)
2016	94 (15)	370 (17)	212 (17)	67 (19)
2017	106 (17)	324 (15)	218 (17)	68 (20)
2018	113 (19)	361 (16)	231 (18)	61 (18)
ASA physical status				
1	1 (0)	5 (0)	9 (1)	0 (0.0)
2	95 (16)	502 (22)	346 (27)	108 (31)
3	454 (74)	1561 (70)	879 (68)	226 (66)
4	60 (10)	169 (8)	53 (4)	11 (3)
5	1 (0)	0 (0.0)	0 (0.0)	0 (0.0)
Surgery classification				
Elective	601 (98)	2213 (99)	1282 (99.6)	343 (99.4)
Urgent	4 (1)	16 (1)	4 (0.3)	2 (0.6)
Emergent	6 (1)	8 (0)	1 (0.1)	0 (0.0)
Surgery duration, min	318 (146)	261 (124)	219 (98)	194 (90)
Type of anaesthesia				

Continued

Table 1 Continued

Factor	Minimum postoperative haemoglobin during the initial 3 postoperative days			
	<8 g dl^{-1}	8–11 g dl^{-1}	11–13 g dl^{-1}	>13 g d^{-1}
	N=611 (14%)	N=2237 (49%)	N=1287 (29%)	N=345 (8%)
General	445 (73)	1687 (75)	1080 (84)	305 (88)
Regional	28 (5)	129 (6)	30 (2)	8 (2)
Combined	138 (22)	421 (19)	177 (14)	32 (10)
AUC of intraoperative MAP <65 mm Hg, in mmHg·min	37 [5, 105]	21 [1.0, 73]	7.0 [0.0, 44]	4.0 [0.0, 29]
Colloids use, %	385 (63)	956 (43)	285 (22)	41 (12)
Tranexamic acid use, %	9 (2)	43 (2)	14 (1)	5 (2)
Crystalloids, L	2.9 [2.1, 4.1]	2.5 [1.7, 3.4]	2.0 [1.3, 2.9]	1.7 [1.2, 2.5]
Estimated intraoperative blood loss, cm^3	300 [100, 700]	100 [40, 275]	50 [20, 100]	30 [10, 75]
Intra- and post-operative RBC transfusion, %	142 (23)	177 (8)	8 (0.6)	0 (0.0)
RBC volume transfused, units	2.0 [1.1, 3.2]	2.0 [1.0, 2.7]	2.2 [1.0, 4.0]	–

≥0.03 ng ml^{-1} until the first of hospital discharge or 3 postoperative days, judged to be of an ischaemic origin. Non-ischaemic aetiologies are detailed in Supplementary Table S1.

Statistical analyses

For data presentation only (not analysis), patients were divided into four groups based on their lowest haemoglobin concentration within the initial 3 postoperative days or before the occurrence of MINS, whichever came first, using clinically common haemoglobin thresholds. Potential confounding factors and incidence of myocardial injury were summarised by the following lowest haemoglobin groups: ≤8, 8–11, 11–13, and ≥13 g dl^{-1}. They were summarised as *N* (%) of patients, means (standard deviations [SD]), or medians [Q1, Q3] for categorical, symmetric continuous variables, and skewed continuous variables, respectively.

Primary analysis

For the primary analysis, we assessed the association between postoperative haemoglobin and MINS using a multiple time-varying Cox proportional hazards model adjusting for all potential confounders in Table 1, including preoperative haemoglobin concentration, age, sex, intraoperative volume of crystalloids administered, and intraoperative and postoperative RBC transfusion. The daily haemoglobin measurement before being censored or having MINS was used as the time-varying exposure. This analysis enabled us to incorporate daily haemoglobin information, and to avoid overlapping issues between events and exposure that could not be solved if logistic regression models were used.

Secondary analysis

A secondary analysis to explore the association between absolute decrease in haemoglobin concentration from preoperative to each postoperative day and MINS was conducted with a time-varying Cox proportional hazards model and two-tailed testing as in the primary analysis adjusting confounders in the primary analysis.

Sensitivity analysis

As we also had a 30 day follow-up for MINS for these participants, which enabled us to potentially capture more events, another time-varying Cox proportional hazards model was used to explore the association of haemoglobin and MINS. The missing haemoglobin measurements between discharge and 30 day follow-up were imputed using a last observation carried-forward algorithm.

Posthoc analyses

We also conducted several separate *posthoc* analyses. Interactions with $P<0.10$ were considered statistically significant. Odds ratios along with 97.5% (Bonferroni-corrected) confidence intervals (CI) were reported separately by each significant factor.

1. Association between postoperative haemoglobin concentration, MINS, and sex.
2. Association between postoperative haemoglobin concentration, MINS, and race.
3. We explored if the relationship between the lowest haemoglobin and outcome was linear by using the restricted cubic spline plot. If this relationship were non-linear, we would add spline terms appropriately.
4. MINS and reduction in haemoglobin after adjusting for iron deficiency anaemia and anaemia of chronic disease.
5. Haemoglobin and myocardial injury in patients with non-ischaemic aetiologies of troponin elevation.

Sample size estimation

Our *a priori* power calculation was based on a logistic regression model. Having 3000 patients available for analysis, with an estimated outcome incidence of only 1%, and an estimated average (standard deviation) minimal postoperative haemoglobin of 10 (2) g dl^{-1}, would have given us 80% power to detect an odds ratio as small as 1.30 per 1 g dl^{-1} decrease in minimal postoperative haemoglobin at the 0.05 significant level. We used an alpha of 0.05 for both primary and secondary analyses. SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.3.2 (R Project for Statistical Computing, Vienna, Austria) were used for all analyses.

Results

Participant characteristics

We identified 6141 patients ≥45 yr old who either had colorectal surgery in the Cleveland Clinic between 2015 and 2018 or had

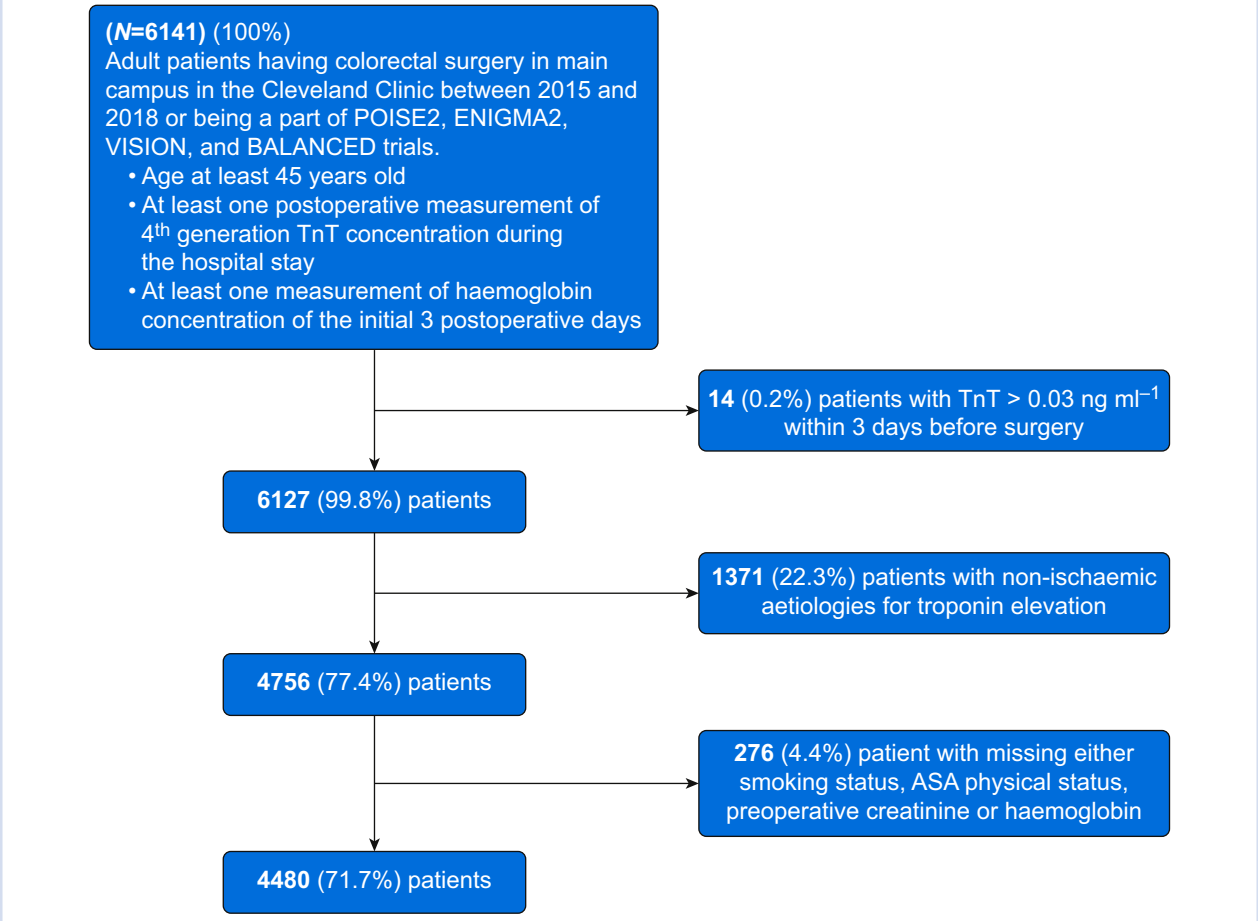

Fig 1. Flowchart of patients. POISE2, PeriOperative ISchemic Evaluation-2 Trial; ENIGMA II, the Safety of Addition of Nitrous Oxide to General Anaesthesia in At-risk Patients Having Major Non-Cardiac Surgery trial; BALANCED, Anaesthetic Depth and Complications After Major Surgery trial; VISION, Vascular Events In Noncardiac Surgery Patients Cohort Evaluation Study.

noncardiac surgery and participated in one of the four trials (POISE2, ENIGMA2, VISION, and BALANCED) with at least one routine postoperative TnT measurement. After excluding patients with preoperative elevated troponin concentrations and patients with non-ischaemic aetiologies for elevated TnT, and patients with missing haemoglobin or baseline data, 4480 patients remained available for our analyses (Fig. 1). Among 4480 eligible patients (Table 1), 91% remained hospitalised on the second day and 76% stayed at least 3 days. Types of surgery are detailed in Supplementary Table S2. Patients had a median of 3 (inter-quartile range [IQR], 2–4) haemoglobin measurements during the initial 3 postoperative days with 3231 (72%) patients having a haemoglobin measure available on the day of surgery, 3439 (77%) patients on postoperative day 1, 2689 (60%) on day 2, and 2113 (47%) on day 3.

Primary outcome

The overall incidence of MINS was 155/4480 (3.5%), ranging from 0/345 (0%) in patients with minimum postoperative haemoglobin greater than 13 g dl^{-1}, to 52/611 (8.5%) in patients with postoperative haemoglobin of less than 8 g dl^{-1} (Supplementary Table S3). The postoperative haemoglobin concentration was inversely associated with hazards of MINS ($P<0.001$), with an adjusted hazard ratio of 1.29 [95% CI, 1.16–1.42] for a 1 g dl^{-1} decrease in haemoglobin concentration (Table 2 and Fig. 2).

Secondary analysis

Our secondary analysis evaluating the association between the difference between preoperative and daily postoperative haemoglobin and the hazards of MINS in a time-varying covariate analysis showed an adjusted hazard ratio of 1.29 [95% CI, 1.16–1.42] ($P<0.001$) for every 1 g dl^{-1} additional reduction from preoperative to postoperative haemoglobin within the 3 postoperative days (Table 2).

Sensitivity analysis

The sensitivity analysis using a follow-up time of 30 days in a time-varying Cox proportional model was consistent with our primary analysis, with an estimated hazard ratio of 1.34 [95% CI, 1.22–1.47] for every 1 g dl^{-1} decrease in haemoglobin concentration.

Table 2 Association between postoperative haemoglobin concentration and the incidence of MINS (N=4480). Observed raw incidence is reported as N (%). CI, confidence interval; MINS, myocardial injury after noncardiac surgery; RBC, red blood cells; HR, hazard ratio.

	N (%)	Exposure	Hazard ratio [95% CI][†]	P-value[*]
Primary analysis				
In-hospital MINS	155 (3.5)	1 g dl^{-1} decrease in haemoglobin	1.29 [1.16, 1.42]	<0.001
Sensitivity analysis				
30 day MINS	184 (4.1)	1 g dl^{-1} decrease in haemoglobin	1.34 [1.22, 1.47]	<0.001
Secondary analysis				
In-hospital MINS	155 (3.5)	1 g dl^{-1} further reduction from preoperative haemoglobin	1.29 [1.16, 1.42]	<0.001

*P-value corresponds to model-based Wald χ^2 tests; significant P-value is less than 0.05.
† Time-varying Cox proportional hazards model was used, and the hazard ratio was reported; results are adjusted for all demographic, baseline comorbidities and medications, and surgical variables listed in Table 1 except for RBC volume among transfused.

Posthoc analyses

Postoperative haemoglobin and sex

We found a significant interaction between postoperative haemoglobin and sex (P=0.034). The association between haemoglobin and MINS was not significant for women, with an estimated hazard ratio of 1.15 [97.5% CI, 0.97–1.36] (P=0.09), but was significant for men, with an adjusted hazard ratio of 1.37 [97.5% CI, 1.20–1.57] (P<0.0001) for every 1 g dl^{-1} decrease in haemoglobin concentration.

Postoperative haemoglobin and race

There was no interaction between postoperative haemoglobin and race (P=0.89).

Preoperative anaemia

The associations between postoperative haemoglobin and MINS were not different across preoperative anaemia groups, with an estimated hazard ratio of 1.31 [95% CI, 1.11–1.54] for patients with preoperative anaemia and 1.30 [95% CI, 1.16–1.45] for patients without preoperative anaemia (P=0.94 for interaction). *Post-hoc* analysis also found that MINS was associated with a hazard ratio of 1.29 [95% CI, 1.17–1.42] with each unit reduction of postoperative haemoglobin after adjusting for iron deficiency anaemia and anaemia of chronic disease in the time-varying Cox model.

Non-ischaemic aetiologies for MINS

For patients with potential non-ischaemic aetiologies for troponin elevations, myocardial injury was associated with a hazard ratio of 1.22 [95% CI, 1.13–1.32] with each unit reduction of postoperative haemoglobin.

Discussion

Preoperative anaemia is a poor prognostic sign and is associated with postoperative cardiac, respiratory, infectious, and wound complications, prolonged hospital and ICU stay, along with mortality.[5,22–24] Our retrospective analysis adds to existing information by demonstrating an independent association between postoperative haemoglobin concentration and the risk of MINS, even after adjusting for many risk factors including baseline haemoglobin. This association was strong, with a 29% hazard increase for each 1 g dl^{-1} decrease in haemoglobin. Remarkably, none of the >340 patients with a minimum postoperative haemoglobin >13 g dl^{-1} had MINS, whereas the incidence was 8.5% in almost 600 patients whose postoperative haemoglobin was <8 g dl^{-1}. Although our analysis was not designed to demonstrate a safe threshold above which the risk is minimal, it appears that MINS is rare in patients who have high postoperative haemoglobin concentrations.

The association between postoperative haemoglobin levels and MINS is intriguing because unlike other risk factors, including baseline cardiovascular risk, haemoglobin concentration is a potentially modifiable factor. Low postoperative haemoglobin concentrations are possibly just a marker for various disease processes that promote myocardial injury. However, it is also plausible that the relationship is causal because most postoperative myocardial injury appears to be largely consequent to myocardial supply–demand mismatch.[4] For example, hypotension is common, profound, and prolonged in patients recovering from noncardiac surgery[25] – and is associated with myocardial injury.[26] Presumably, hypotension is especially likely to compromise myocardial perfusion in patients who are also anaemic. To the extent that low haemoglobin is causally related to inadequate perfusion,

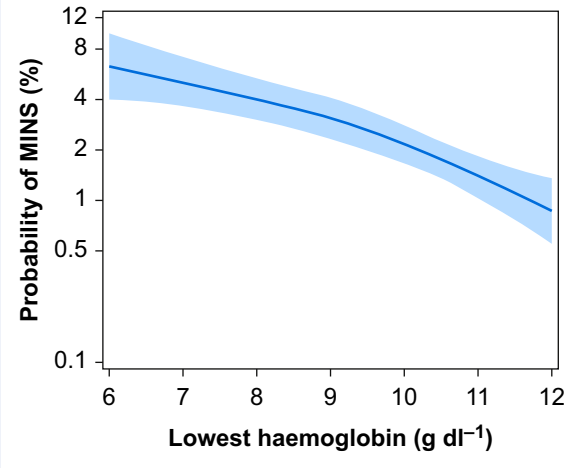

Fig 2. The relationship between probability of having myocardial injury after noncardiac surgery (MINS) and lowest haemoglobin during postoperative 3 days. The solid line represents the predicted adjusted probability of having MINS and the blue band was the corresponding confidence interval.

preventing postoperative anaemia might also prevent myocardial injury.

An apparent difficulty with postulating a causal relationship between anaemia, with or without hypotension, and myocardial injury is that there have been several randomised trials evaluating various transfusion thresholds. In most trials,[11,13,27,28] but with few notable exceptions,[17,29,30] lower transfusion thresholds have not worsened outcome. The difficulty, though, is that all these trials compare only slightly different transfusion thresholds such as haemoglobin concentrations of 9 *vs* 7 g dl^{-1}. As most patients in such trials do not require transfusions, haemoglobin concentrations usually do not much differ in patients assigned to higher and lower transfusion thresholds. For example, in the three largest transfusion trials in noncardiac surgery, the haemoglobin concentrations differed by only 1.3,[27] 0.9,[13] and 1.1 g dl^{-1}.[17] With such small differences in haemoglobin, it is unsurprising that outcomes were similar. An additional consideration is that transfusions may themselves be harmful,[9,10] thereby offsetting the potential benefit of increasing haemoglobin. A final consideration is that none of the randomised trials specifically evaluated myocardial injury. As more than 90% of postoperative myocardial injury is asymptomatic,[3] we can assume that nearly all injuries were missed in these trials. Although the serious outcomes evaluated by these studies are clinically important, evaluating myocardial injury can shed more light on the underlying risk factors leading to the serious outcomes.

A strength of our design is that we only included patients who had scheduled monitoring of postoperative troponin concentrations. Some participated in various trials, all of which enrolled patients ≥45 yr old; others had routine troponin monitoring, mostly according to age and baseline cardiovascular risk. We therefore did not have to assume that patients without troponin measurements did not have MINS. A consequence is that our cohort included patients who were at cardiovascular risk, and our results should be interpreted in this light.

Our primary analysis tested the association between postoperative haemoglobin and MINS while adjusting for RBC transfusions, although transfusion might also serve as a mediator. For example, low haemoglobin concentrations increase the chances of RBC transfusions, and transfusion of allogeneic blood might contribute to MINS via inflammation and increased platelet aggregation. We nonetheless adjusted for transfusions in our primary analysis to evaluate the relationship between postoperative haemoglobin levels and MINS. To the extent that transfusions are a mediator of postoperative haemoglobin, adjusting for them would diminish the apparent association between postoperative haemoglobin and MINS.

Transfusions increase haemoglobin concentrations, but it remains unclear whether the association between postoperative haemoglobin and myocardial injury is causal, and thus potentially modifiable. Furthermore, treatment with blood transfusions is costly and may introduce a different set of risks. Other methods of increasing or preserving red cells (such as erythropoietin treatment and blood preservation techniques) each have their own risks and costs. An additional consideration is that we only evaluated MINS. Although MINS is associated with postoperative mortality, there are obviously many other contributing factors that may or may not be related to anaemia.

Our analysis has several potential limitations. More than 90% of 30 day MINS occurs within the initial 2 postoperative days.[3] We thus restricted our analysis to the initial 3 postoperative days. A consequence of conducting a registry analysis is that we could not mandate haemoglobin determinations. However, all included patients remained hospitalised at least overnight, and most stayed at least 2 days. In general, haemoglobin is measured daily at the Cleveland Clinic in postoperative patients deemed sick enough to require hospitalisation. Haemoglobin concentration can change over the initial postoperative days as vascular volume normalises, or because of internal bleeding, as is common in hip arthroplasties. However, our time-varying cox proportional model for the primary analysis considered the temporal relationship between haemoglobin determinations on detection of MINS.

Another limitation is that we used fourth-generation TnT measurements, as this was the troponin used at our centre during the conduct of this study. The definition of MINS for fourth-generation troponin which we used in the current analysis does not consider changes from preoperative levels. Therefore, preoperative troponin evaluations were not mandatory or routine, and thus, we could not consistently exclude patients with increased preoperative TnT concentrations. We did, however, exclude patients with troponin elevations that could be considered of non-ischaemic aetiologies (e.g. stroke, sepsis, pulmonary embolism).

Our analysis was retrospective and thus limited by type and quality of data available in medical records, and residual confounding. The population tested is heterogenous, consisting of patients undergoing relatively minor procedures but having anaemia of chronic disease, whereas others had major surgeries with acute bleeding and need for transfusions. We made an effort to control for many patient- and surgery-related characteristics via a Cox proportional hazards model to minimise confounding, but at least some confounding surely results from unmeasured factors. We reduced measurement bias by only including patients who had troponin measured routinely as a part of clinical practice or a clinical trial.

In summary, we observed a strong association between postoperative haemoglobin concentration and myocardial injury. Whether this relationship is causal remains to be determined, but it is plausible because myocardial supply–demand mismatch appears to promote postoperative myocardial injury.

Authors' contributions

Study concept: AT, BC
Study design: AT, BC, ER, NM, KM, EF, OO, JW, KR, PJD, DIS
Data analysis: AT, BC, ER, NM
Data interpretation: AT, BC, ER, NM, KM, EF, OO, JW, KR, PJD, DIS
Drafting of the manuscript: AT, BC, ER, NM, KM, EF, OO, JW, KR, PJD, DIS
Critical revision of the manuscript: AT, BC, ER, NM, KM, EF, OO, JW, KR, PJD, DIS

Declarations of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.08.056.

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