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Acute Surgical Anemia Influences the Cardioprotective Effects of β-Blockade

A Single-center, Propensity-matched Cohort Study

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ABSTRACT

Background: Despite decreasing cardiac events, perioperative β-blockade also increases perioperative stroke and mortality. Major bleeding and/or hypotension are independently associated with these outcomes. To investigate the hypothesis that β-blockade limits the cardiac reserve to compensate for acute surgical anemia, the authors examined the relationship between cardiac events and acute surgical anemia in patients with and without β-blockade.

Methods: The records of all noncardiac, nontransplant surgical patients between March 2005 and June 2006 were retrospectively retrieved. The primary outcome was a composite that comprised myocardial infarction, nonfatal cardiac arrest, and in-hospital mortality (major adverse cardiac event). The lowest recorded hemoglobin in the first 3 days defined nadir hemoglobin. Propensity scores estimating the probability of receiving a perioperative β-blocker were used to match (1:1) patients who did or did not receive β-blockers postoperatively. The relationship between nadir hemoglobin and major adverse cardiac event was then assessed.

Results: This analysis identified 4,387 patients in whom nadir hemoglobin could be calculated; 1,153 (26%) patients were administered β-blockers within the first 24 h of surgery. Propensity scores created 827 matched pairs that were well balanced for all measured confounders. Major adverse cardiac event occurred in 54 (6.5%) β-blocked patients and in 25 (3.0%) β-blocker naive patients (relative risk 2.38; 95% CI 1.43–3.96; $P = 0.0009$). The restricted cubic spline relationship demonstrated that this difference was restricted to those patients in whom the hemoglobin decrease exceeded 35% of the baseline value.

Conclusions: β-Blocked patients do not seem to tolerate surgical anemia when compared with patients who are naive to β-blockers. Prospective studies are required to validate these findings.

What We Already Know about This Topic

- Perioperative β-adrenergic blockade may reduce risk of myocardial infarction but may also increase risk of perioperative stroke and mortality, especially with major blood loss

What This Article Tells Us That Is New

- In a retrospective review of noncardiac surgery patients, a composite of major cardiac complications and mortality was increased in β-blocked patients with more than 35% drop in hemoglobin concentration, and β-blocked patients may not tolerate surgical anemia

THE 2007 updated guidelines of the American College of Cardiology/American Heart Association, for the prevention of cardiac morbidity in noncardiac surgery, gave proceeding to surgery with "heart rate control"—a Class IIa recommendation in patients with clinical risk factors.[1] The overwhelming results of randomized trials show that perioperative β-adrenergic antagonism decreases cardiac morbidity and mortality. However, many of these same trials have raised safety concerns, showing increased stroke rates and total mortality.[2,3] The safety issues relate to a universal finding that these agents are associated with an increased incidence of bradycardia and hypotension. The Perioperative Ischemic Evaluation (POISE) trial[4] assessed metoprolol,

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◆ This article is accompanied by an Editorial View. Please see: Weiskopf RB: Perioperative use of β-adrenergic antagonists and anemia: Known knowns, known unknowns, unknown unknowns; and unknown knowns. ANESTHESIOLOGY 2010; 112:12–5.

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started on the day of surgery, in patients naive to β-blockers. The POISE study showed that 45% of the deaths were associated with hypotension and significant bleeding.

We would suggest that acute surgical anemia may be a link between these two factors. Note that up to 30% of patients have preoperative anemia,[5] and as many as 50% of surgical patients experience a drop in hemoglobin to less than 90 g/l. Furthermore, anemia is associated with increased mortality.[5,6] Anemia induces a cardiovascular response, and increasing cardiac output is mediated through a combination of increased stroke volume and heart rate. However, when hemoglobin decreases to 90 g/l, the ability to increase stroke volume is reduced or "plateaus," and further increases in cardiac output are solely heart rate dependant.[7] Thus, patients with attenuated ability to mount a cardiac response to the anemic stress will become hypotensive.

This creates an interesting paradox; as we have outlined, patients in whom the hemoglobin decreases to less than 90 g/l require a tachycardia to maintain oxygen delivery. Conversely, tachycardia, of this magnitude, has been associated with ongoing and prolonged perioperative ischemia. Prolonged ischemia leads to an increased incidence of perioperative myocardial infarction (MI).[8] Recent meta-regression analyses suggest that the cardioprotective effects of β-blockers ensue only where stress-mediated tachycardia is attenuated.[9,10] Thus, acute anemia in β-blocked patients could explain some of the safety issues that have arisen as the result of prospective β-blocker trials.

The purpose of this study was to compare the effect of acute anemia on adverse cardiovascular outcomes in two propensity score-matched cohorts; one was a perioperatively β-blocked cohort and the other cohort matched for cardiac, respiratory, and hematologic risk factors did not receive perioperative β-blockers.

Materials and Methods

Study Setting, Patient Sample, and Data Collection

This article was prepared to conform to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[11] The Toronto General Hospital is a tertiary referral center in Toronto, Ontario, affiliated with the University of Toronto. Noncardiac surgical services at this institution include vascular and oncology surgery in head and neck, urology, thoracic, hepatobilary, general, and gynecologic procedures. After obtaining Institutional Research Ethics Board approval, data were retrospectively collected on 5,064 consecutive adult patients (> 18 yr) who underwent major noncardiac surgery. Patients were identified from the ORSOS (McKesson Corporation, San Francisco, CA) surgical bookings from March 2005 to June 2006. We specifically excluded all patients having cardiac surgery, solid organ transplantation (due to increased risk), and same day discharge patients (due to very low risk[12]). This dataset thus represents all elective and emergent noncardiac surgical procedures. We excluded all patients with a preoperative hemoglobin of 90 g/l or less ($n = 356$). For patients who underwent more than one relevant procedure during the study period, only their initial surgery was included for analysis ($n = 45$). Perioperative data and outcomes were collected from existing clinical databases and the patient charts.

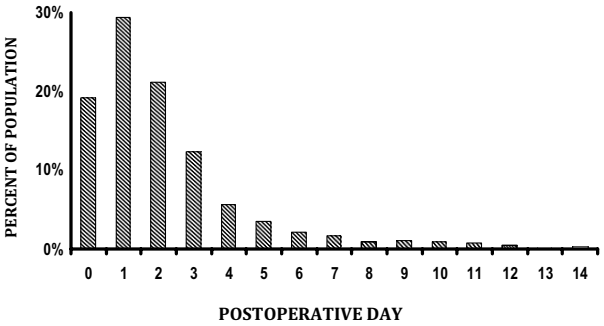

Fig. 1. Distribution of nadir hemoglobin by day of surgery. Eighty-two percent of patients experienced the nadir hemoglobin in the first 3 postoperative days. In this analysis, there was no fixed schedule for measurement of hemoglobin. Thus, nadir was taken as the lowest recorded level in that time period.

Synthesis and Linking of Electronic Databases

Data, including demographics and laboratory tests, were retrieved from the electronic data warehouse by using previously published methodology.[13] The nature of surgery and preoperative comorbidities were downloaded from the hospital electronic charting system (MISYS CPR; Quadramed Corp, Reston, VA). Laboratory tests were retrieved from the laboratory data warehouse. We specifically downloaded the daily maximum or minimum values for troponin, hemoglobin, creatinine, and glucose for the first seven postoperative days. Because there was no routine for the postoperative measurement of hemoglobin, we arbitrarily defined nadir hemoglobin as the lowest level seen in the first 3 days after surgery. This time period accounted for more than 85% of the lowest recorded postoperative hemoglobin levels (fig. 1). We excluded all patients in whom postoperative hemoglobin level was not obtained ($n = 275$). This left a final evaluable population of 4,378 patients. Details of all medications were retrieved from the Pharmacy database (PYXIS®, Pyxis Corp., San Diego, CA). This allows for the retrieval of drug, dose, time, and date of administration; this system does not allow for retrieval of intraoperative administration of any drug. We extracted details of all β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, statins, analgesics including nonsteroidal antiinflammatory drugs, and opiates and heparins. For the purposes of this analysis, perioperative β-blockade was defined as having β-blockers administered (either orally or intravenously) within 24 h of surgery. We based this decision on the observation in POISE that the highest frequency of postoperative MI occurred in the first 24 postoperative hours. Detailed blood product transfusions were manually retrieved from the blood bank database (Hemocare®; Mediware Information Systems Inc., Lenexa, KS) including the amount and time of red blood cells, plate-

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lets, fresh frozen plasma, and cryoprecipitate. In-hospital mortality was assessed using the hospital discharge dataset. Data were merged by using the patients unique identifying number, the dates of surgery, and collated in a separate electronic database for further analysis.

Primary Outcome

The primary outcome for this analysis was major adverse cardiac events, and a composite outcome comprised MI, nonfatal cardiac arrest, and in-hospital mortality. Troponin I was measured during the entire study period, using the Dade Behring Dimension assay (Siemens Healthcare Diagnostics, Deerfield, IL). The lower limit of reporting is less than 0.2 μg/l reflecting the functional sensitivity of the assay, which has a 10–20% coefficient of variance. We defined an MI as any increase of troponin I more than 0.7 μg/ml. In the positive range, the coefficient of variation is approximately 5%. Cardiac arrest and in-hospital mortality, up to 30 days postoperatively, were retrieved by using the 10 codes of the World Health Organization International Classification of Diseases entered at the time of discharge.

We assessed the relationship between percent decrease in the preoperative hemoglobin and the probability of having the composite ischemic outcome using the restricted cubic spline function. We assessed this relationship in each in the two propensity score—matched cohorts: one was a sample population taking β-blockers, and the second was a sample population, with a similar risk profile, who were not taking β-blockers. We used the cubic splines to assess whether dichotomization of hemoglobin drop was appropriate in its relation to the outcome. Assuming that this is the case, this association was further assessed with the use of chi-square and logit estimates of odds ratio, and the results contrasted between β-blocked and control patients.

Statistical Analyses

SAS version 9.1 (SAS Institute, Inc., Cary, NC), was used for all statistical analyses. Categorical variables were summarized as frequencies and percentages and continuous variables as means and SD.

Propensity Score Matching of Cohorts

Propensity scores estimating the probability of receiving a perioperative β-blocker were calculated for all patients. In the nonparsimonious multiple logistic regression model for the propensity score, the following covariates were used: age (dichotomized at 70 yr), gender, International Classification of Disease 10 codes for a preoperative history of coronary disease (using the codes for stable angina and history of MI), congestive heart failure, diabetes (Type I or II), and renal disease defined as a preoperative creatinine of greater than 175 mM. (A revised cardiac risk index was calculated for each patient.) In addition, the conditions included were cancer, chronic obstructive pulmonary disease, and hypertension. The hematologic variables included preoperative hemoglobin and transfusion on the day of surgery (expressed in three categories: no transfusion, 1–3 units, 4 and more units). The logistic model also included nonsteroidal antiinflammatory drug, calcium channel blockers, angiotensin-converting enzyme inhibitors, acetylsalicylic acid, statins, and heparins. Finally, high risk surgeries, either thoracic or vascular, were forced into the model. Individual patients taking β-blockers were matched 1:1 to patients who did not receive β-blockers postoperatively on the basis of similar matched propensity scores.[14] A 5←1 computerized greedy matching technique was used for this matching process whereby cases were first matched to controls that had a propensity score (logit transformation) that was identical in all five digits. Those that did not match were then matched to controls on four digits of the propensity score. This continued down to a 1-digit match on propensity score for those that remained unmatched.††

If after the matching one or more variables remained unbalanced, interaction terms were included in the model. This iterative procedure continued until the matched cohorts were balanced for the baseline covariates.

We assessed the ability of the model to balance the two cohorts by using a standardized mean difference. Standardized difference (d) is defined to be equal to

$$d = \frac{100 \cdot (\bar{x}_{treatment} - \bar{x}_{control})}{\sqrt{\frac{s^2_{treatment} + s^2_{control}}{2}}},$$

where $\bar{x}_{treatment}$ and $\bar{x}_{control}$ are the mean values for the treatment and control groups, whereas $s^2_{treatment}$ and $s^2_{control}$ are the sample standard deviations, respectively. Differences of absolute value greater than 10% are considered to indicate significant covariate imbalance.[15]

The association of β-blocker to the outcomes was tested with the use of conditional logistic regression. The relationship between hemoglobin drop and probability of the outcome was explored with the use of cubic splines.

Sensitivity Analyses

We carried out two *post hoc* sensitivity analyses: the first on the effect of perioperative blood transfusion, and the second was for the effect of troponin measurment.

Our hypothesis was that acute anemia increases ischemic outcomes and that this response would be worse in β-blocked patients because they are unable to mount a cardiac response. Thus to show that this effect was independently associated with ischemic outcomes, we had to balance the effect of transfusion between the two arms. However, clinically, the decision to transfuse reflects a complex interrelationship of factors: if the patient becomes ischemic or

†† Parsons LS: Reducing bias in a propensity score matched-pair sample using greedy matching techniques. In: Proceedings of the Twenty-Sixth Annual SAS Users Group International Conference, Cary, NC, 2001.

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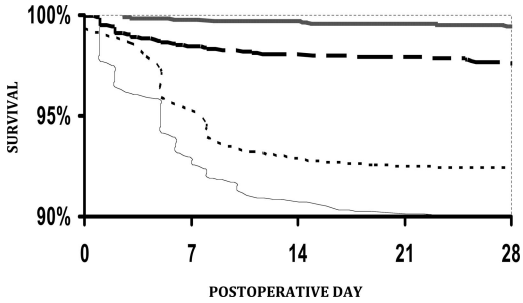

Fig. 2. Survival analysis for the unadjusted population. The in-hospital mortality up to 30 days is represented in 4 groups; (1) the population in whom there was a positive troponin ($n = 119$) is shown in the *bottom line unbroken black line* (troponin I ≥ 0.7 μg/l). (2) The cohort in whom troponin I was < 0.07 μg/l and > 0.02 μg/l ($n = 96$) is shown in the *dotted line*. (3) The population in whom measured troponin I was not detected ($n = 1{,}176$) is shown in the *thick dotted line*. (4) The population in whom troponin was not measured is shown in the *top thick solid line*. This analysis shows that there is increased mortality in patients where troponin was ordered but not detected compared with patients in whom troponin was *not* ordered (relative risk 2.4; 95% confidence interval 1.8–3.4).

hypotensive and if the patient is anemic, one of the first considerations would be to transfuse blood earlier than normal (before reaching a predetermined or personal transfusion trigger), thus mitigating the chance that the ischemic response was induced by hypovolemia or anemia. In addition, we also wanted to mitigate the potential criticism that transfusion of stored blood is independently associated with postoperative mortality.[16] Our primary analysis achieved balance for transfused blood products on the day of surgery; we thus conducted a separate analysis, in which transfusion was not forced into the relationship. In this analysis, we considered transfusion as an outcome, and we assessed the effect of β-blockers with the use of conditional logistic regression.

The second sensitivity analysis was conducted because we found that the measurement of troponin was not evenly distributed between the two cohorts after propensity score balancing for all other variables. On initial consideration, it should be obvious that the imbalance of measuring troponin introduces a detection bias for MI (if troponin is not measured there is a reduced chance, which can not be quantified, of detecting a MI). On further analysis, we found that the mere act of ordering the assay even where troponin I was not detected (fig. 2) was associated with increased relative risk (RR) of both in-hospital and 1-yr mortality compared with patients who did not have it measured. Therefore, we felt that ordering the assay could be the result of intraoperative events (which would suggest that ordering troponin was the result of an outcome) or due to the treating physician's intuition of risk (which means that ordering troponin postoperatively should be treated analytically as a marker of increased comorbidities). The initial analysis was not set up to balance the ordering of troponin between the two groups; this sensitivity analysis assessed the effect of β-blockers on MI after equalizing troponin measurement in both cohorts.

Results

The patient characteristics before and after propensity score matching are listed in table 1. Patients taking β-blockers were potentially at a higher risk of postoperative morbidity. The following comorbidities were seen more frequently in β-blocked patients: hypertension, diabetes (and higher blood glucose levels), renal failure, coronary artery disease, peripheral vascular disease, and congestive heart failure. We also demonstrated that β-blocked patients took more concomitant medications, including calcium channel blockers, angiotensin-converting enzyme inhibitors, aspirin, and statins. β-Blocker use was also associated with more preoperative anemia and lower platelet counts with the expected increase in perioperative transfusions. The unadjusted risk of the composite outcome was seven times greater in the β-blocker group.

Decreased Differences after Propensity Score Matching

The results of the matching algorithm can also be seen in table 1. The algorithm matched 827 of the 1,153 β-blocked patients (71.7%) to the cohort of similar propensity scores. The matching process achieved a good balance between the two groups with respect to comorbidities, drugs, laboratory values, and high risk surgery; there were no categories where the standardized difference (d) was greater than 10%. As an example, the number of patients with a nadir hemoglobin of less than 90 g/l were greater in those receiving β-blockers; this difference was diminished by propensity matching (β-blockers 34.1% *vs.* 32.5% control; $d = 4.2\%$; fig. 3), and the median nadir hemoglobin was 95 g/l in both groups after propensity score matching. All the individual outcomes that comprised our composite outcome were numerically greater in the β-blocked group. There were more patients with postoperative cardiac arrest and more deaths after 30 days. The incidence of these outcomes was low, the number of events was small, and thus this analysis lacks the power to show that individual differences were statistically significant. MI, as measured by postoperative troponin, occurred more often in the β-blocked population (42 β-blocked patients *vs.* 11 control patients $P < 0.0001$). The resultant composite outcome occurred in 54 β-blocked patients and 25 naive patients (RR2.38; 95% CI 1.43–3.96; $P = 0.0009$).

Sensitivity Analysis

In the first sensitivity analysis, we forced neither Day 0 nor postoperative transfusions into the propensity score model. The risk ratio of the composite ischemic outcome slightly increased (2.68 *vs.* 2.38). In this sensitivity analysis, we treated the transfusions as outcomes and tested their associations with β-blockers. The amount of transfusion (Day 0 or total of Days 1–7) were not found to be associated with β-blocker use ($P = 0.24$.).

In the second sensitivity analysis, where our propensity matching algorithm was programmed to force an equalized number of troponin measurements, the increased incidence of MI was retained (RR 1.94; 95% CI 1.09–3.46; table 2).

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Table 1. Patient Characteristics before and after Propensity Score Matching

	Entire Sample			Propensity-matched Cohort		
	β-Blocker (*N* = 1153)	No β-Blocker (*N* = 3234)	*d*	β-Blocker (*N* = 827)	No β-Blocker (*N* = 827)	*d*
Demographics						
Age > 70 yr	493 (42.8)	589 (18.2)	55.3	320 (38.7)	344 (41.6)	−5.9
Height (cm)	167.0 (17.1)	167.6 (16.6)	−3.9	167.3 (16.5)	167.7 (17.1)	−2.4
Weight (kg)	76.9 (19.7)	75.4 (18.2)	8.1	77.5 (20.1)	76.1 (17.9)	7.4
Gender (% male)	688 (59.7)	651 (51.1)	17.4	482 (58.3)	496 (60.0)	−3.5
Preoperative comorbidities						
Hypertension	387 (33.6)	298 (9.2)	62.2	214 (25.9)	218 (26.4)	−1.1
COPD	64 (5.6)	155 (4.8)	3.4	44 (5.3)	43 (5.2)	0.5
Cancer	688 (59.7)	2,298 (71.1)	−24.1	567 (68.6)	592 (71.6)	−6.6
Diabetic	267 (23.2)	244 (7.5)	44.4	144 (17.4)	148 (17.9)	−1.3
Coronary	112 (9.7)	33 (1.0)	39.3	44 (5.3)	31 (3.8)	7.6
Stroke	19 (1.7)	13 (0.4)	12.4	10 (1.2)	9 (10.9)	1.1
CHF	52 (4.5)	16 (0.5)	26.0	11 (1.3)	13 (1.6)	−2.0
Renal failure	67 (5.8)	39 (1.2)	25.2	28 (3.4)	34 (4.1)	−3.8
RCRI 0	506 (43.9)	2,233 (69.1)	−52.5	451 (54.5)	481 (58.2)	−7.3
RCRI 1	446 (38.7)	915 (28.3)	22.2	296 (35.8)	279 (33.7)	4.3
RCRI 2	161 (14.0)	71 (2.2)	44.2	67 (8.1)	55 (6.7)	5.6
RCRI 3	31 (2.7)	14 (0.4)	18.3	11 (1.3)	11 (1.3)	0.00
RCRI 4	7 (0.6)	1 (0.1)	10.3	2 (0.2)	1 (0.1)	2.8
RCRI 5	2 (0.2)	0 (0)	5.8	0 (0)	0 (0)	0.00
High-risk surgery						
Thoracic surgery	162 (14.1)	680 (21.0)	−18.4	145 (17.5)	121 (14.6)	7.9
Vascular surgery	220 (19.1)	78 (2.4)	55.9	89 (10.8)	70 (8.5)	7.8
Medications						
Ca channel blockers	331 (28.7)	251 (7.8)	56.4	181 (21.9)	188 (22.7)	−2.0
ACE inhibitors	391 (33.9)	324 (10.0)	60.3	218 (26.4)	207 (25.0)	3.0
Statins	463 (40.2)	321 (9.9)	74.5	237 (28.7)	236 (28.5)	0.3
NSAIDS	367 (31.8)	1,846 (57.1)	−52.5	312 (37.7)	305 (36.9)	1.8
Aspirin	419 (36.3)	163 (5.0)	83.8	169 (20.4)	149 (18.0)	6.1
Antiemetics	704 (61.1)	1,992 (61.6)	−1.1	506 (61.2)	494 (59.7)	3.0
Acetaminophen	879 (76.2)	2,498 (77.2)	−2.4	616 (74.5)	628 (75.9)	−3.4
Heparins	791 (68.6)	1,945 (60.1)	17.7	547 (66.1)	568 (68.7)	−5.4
Laboratory						
Preoperative hemoglobin (gm/l)	126.1 (19.4)	131.3 (18.5)	−27.4	127.5 (19.1)	127.2 (19.0)	1.9
PRBC Day 0	0.4 (1.3)	0.2 (0.86)	19.4	0.4 (1.1)	0.4 (1.0)	−1.1
PRBC total 1–7	0.3 (1.2)	0.1 (0.7)	21.0	0.3 (1.1)	0.2 (0.7)	10.1
Platelet count	215 (98)	233 (91)	−18.4	222 (102)	224 (100)	−2.4
Glucose	7.2 (3.6)	6.2 (2.3)	31.8	6.9 (3.5)	6.7 (3.)	6.6
Outcomes						
Cardiac arrest	12	7	10.38	7	3	6.32
Postoperative MI	96	23	37.31	42	11	21.41
In-hospital 30-day mortality	28	26	12.96	19	13	5.30
MACE	116	46	37.80	54	25	16.52*

MACE is the composite of cardiac arrest, myocardial infarction, and in-hospital death. Some patients may have had more than one outcome but are only counted once in the composite outcome.

* $P = 0.0009$ comparing control patients to the beta blocked patients.

ACE = angiotensin-converting enzyme inhibitor; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; MACE = major adverse cardiac event; MI = myocardial infarction; NSAIDS = nonsteroidal antiinflammatory drug; PRBC = packed red blood cells; RCRI = revised Cardiac Risk Index.

Hemoglobin Drop and Ischemic Outcomes

The relationship between drop of hemoglobin (expressed as the percent change from the preoperative hemoglobin) and the composite ischemic outcome is seen in figure 4. We compared this relationship between β-blocked patients and a propensity score-matched cohort of patients not taking β-blockers. We found that the relationships were virtually identical until the hemoglobin had decreased by 35% of the baseline level. This analysis shows that β-blockers were associated with a greater incidence of the composite outcome when the decrease in hemoglobin exceeded 35%. The preoperative hemoglobin and the incidence of World Health Organization defined anemia were the same in each group of patients. (We excluded patients with preoperative hemoglobin less that 90 g/l.) A decrease in hemoglobin of more that 35% resulted in a greater incidence of major adverse cardiac event than in patients who did not experience the decrease (RR for β-blockers 3.15; 95% CI 1.8–5.5; $P <$

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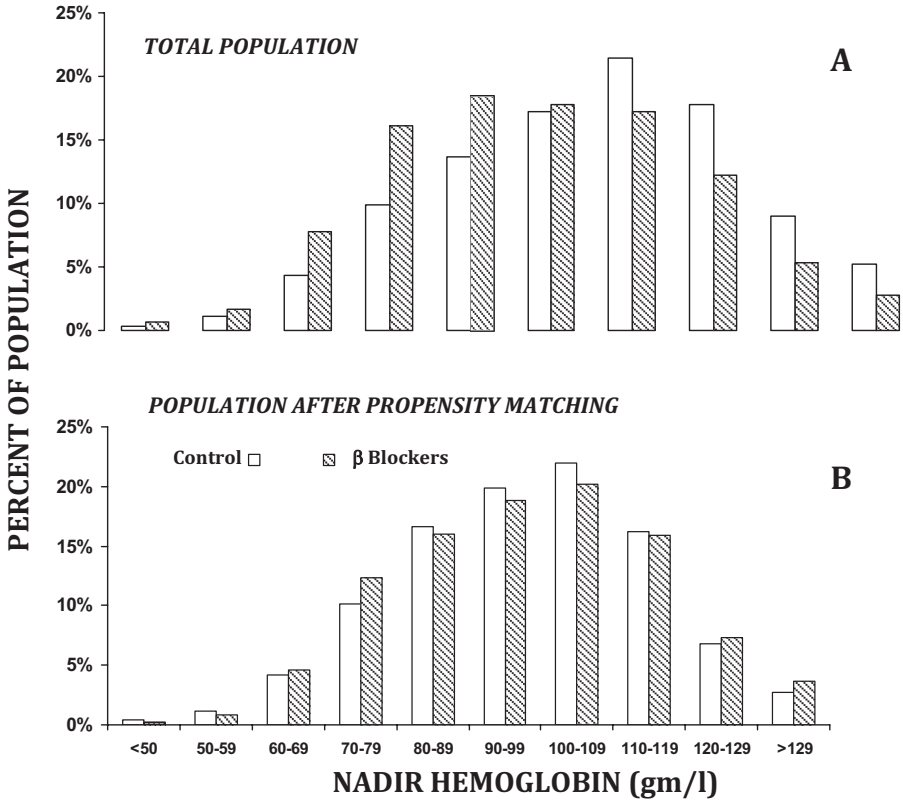

Fig. 3. Frequency plot of nadir hemoglobin. This graph represents the nadir hemoglobin (lowest recorded hemoglobin in the first 3 postoperative days) in the 2 cohorts (*open bars* are control and *hatched bars* represent β-blocked patients) before propensity matching (*A*) and after matching (*B*). Note that β-blocked patients have proportionally more patients with nadir hemoglobin (in the first 3 postoperative days) less than 90 mg/l in (*A*) (the unadjusted population). Propensity matching seen in (*B*) results in two balanced populations ($d = 3.87$) A nadir hemoglobin less than 90 mg/l was associated with a troponin measured two times more frequently than nadir hemoglobin more than 90 mg/l (relative risk 1.9; 95% confidence interval [CI] 1.6–2.2). This increased use of troponin testing was seen irrespective of whether the patients were β-blocked or not. In the patients with a nadir hemoglobin less than 90 mg/dl, β-blockade was associated with a 3-fold increase in myocardial infarction (relative risk 2.94; 95% CI 1.4–6.4).

0.0001, and in non-β-blocked patients, this did not achieve significance RR 2.17; 95% CI 0.97–4.86; $P = 0.0533$). This relationship was essentially the same in the sensitivity analyses.

Discussion

This investigation suggests that acute surgical anemia, expressed as a greater than 35% drop on preoperative hemoglobin, increases major acute coronary morbidity. The analysis further suggests that the relationship is worse in patients taking β-blockers. We did not demonstrate that β-blockers were harmful when the perioperative hemoglobin levels were within 30–35% of the baseline hemoglobin levels. These relationships were not altered in our sensitivity analyses, where transfusions were not balanced but the measurement of troponin was balanced.

Table 2. Sensitivity Analyses

	Patients after PS Matching	Mean Standardized Difference in the PS Model	Relative Risk of MACE* (95% CI)	*P*
Primary analysis	827	0.9 ± 4.7	2.38 (1.43–3.96)	0.0009
Transfusions not in PS model	817	1.4 ± 4.4	2.68 (1.58–4.55)	0.0002
Troponin measurements balanced†	795	0.09 ± 3.0	1.94 (1.09–3.46)	0.021

* MACE is the combined outcome of cardiac arrest, myocardial infarction, and in-hospital death. † MACE results are predominately driven by increased myocardial infarction and an imbalance in the rates of performing the test bias the probability of finding an outcome. However, the act of ordering a troponin is in fact an outcome, based on patient characteristics and other events. In this analysis, we measured the effect of balancing troponin (to balance the probability of finding an myocardial infarction) and measures the effect on increased troponin.

MACE = major adverse cardiac event; PS = propensity score.

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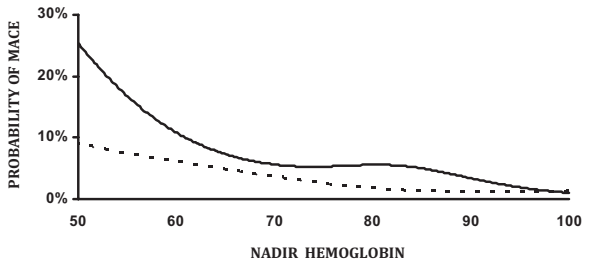

Fig. 4. Restricted cubic spline relationship between nadir hemoglobin and the probability of the primary outcome. The X axis represents the lowest recorded hemoglobin within 3 days of the index surgery expressed as a percent of preoperative hemoglobin. The Y axis is the probability of the combined outcome. Major adverse cardiac event is the combined outcome of myocardial infarction (troponin I elevation $\geq$ 0.7 μg/l), cardiac arrest, and in-hospital death. β-Blocked patients are represented by the *solid line*.

Mild to moderate normo-volemic hemodilution (defined as a decrease in baseline hemoglobin of less than 30%) has been shown to induce an increase in cardiac output that is in direct relationship to the degree of dilution. The increase in cardiac output is accomplished by a combination of increased stroke volume, heart rate, and a reduction in peripheral resistance.[7] The ability of increased stroke plateaus at hemoglobin between 90 and 100 g/l creates situations where any further decrease in hemoglobin (to less than 90 g/l) will render all further compensatory increases in cardiac output heart rate dependant. A later publication reproduced these findings showing that the major response to hemodilution is a tachycardia, and the chronotropic response is linearly proportional to the degree of hemodilution. Perioperative physicians are being encouraged to tolerate lower hemoglobin and triggering transfusion at levels approaching 70 g/l.[17] As a result, moderate hemodilution is common during noncardiac surgery. In this cohort, nadir hemoglobin was less than 75 g/l in 11% of the patients and less than 90 in 32% of all patients. In addition, preoperative anemia is common, as seen in more than 25% of patients having major elective surgery, and it has also been independently associated with increased postoperative mortality.[5,6]

Perioperative MI is a leading cause of postoperative mortality. ST segment elevation infarctions (type l) occurred in less than 2% of the perioperative patients studied.[8] Many perioperative MIs are classified as type II with relation to supply/demand imbalance.[18] The peak incidence within the first 48 postoperative hours, frequently less than 24 h, and troponin increases are usually preceded by a prolonged period of ischemia. Tachycardia is believed to be one of the most common causes of increased myocardial oxygen demand. β-Blockers have little or no effect on stroke volume in stress-testing models.[19] Hence, the physiologic basis for the cardioprotective effect of β-blockers resides mostly in the ability to limit heart rate. Indeed, meta-regression of the available clinical studies has suggested the best cardioprotective effects stem from studies with the greatest attenuation of the chronotropic response to stress.[9]

The American College of Cardiology/American Heart Association 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery state that "β-blockers are probably recommended for patients in whom perioperative assessment identifies CHD [heart disease] of high cardiac risk as defined by the presence of more than one clinical risk factor who are undergoing intermediate risk of vascular surgery (Class IIa, level of evidence B)." The recent publications of larger β-blocker trials have raised serious doubts about the safety of perioperative β-blockers.[20,21] Metoprolol succinate, started on the day of surgery, was associated with a 30% reduction in MIs. Conversely, it increased total mortality by 30%, and postoperative strokes, while rare, were doubled. POISE showed that hypotension, which was an independent predictor of death, MI, and stroke, occurred in 12% of all patients.[4] β-Blocker therapy was associated with 61% of the hypotensive episodes. A major cause of perioperative hypotension is blood loss, hypovolemia, and/or inadequate fluid resuscitation or a blunted cardiovascular response to anemia. Our analysis supports the hypothesis that acute surgical anemia elicits a cardiovascular response and further that β-blockade attenuates this response, exposing the patient to increased risk.

Our results show that the safe level of hemodilution is different in β-blocked than in nontreated patients. Readers should note that the point of divergence between β-blocked and control patients in or propensity analysis and sensitivity analyses is at a hemodilution of 25–30% of the baseline. This degree of dilution corresponds with the level of hemoglobin where stroke volume plateaus and further increments of cardiac output become heart rate dependant. Alternatively, this deleterious effect was not observed when hemodilution was limited to less than 30% of preoperative levels.

Comparison with Other Studies

The results of this investigation differ from most of the prospective randomized trials[2,3] in that our analysis did not show a cardioprotective effect (reduced MI). We would point out that for patients with nadir hemoglobin more than 90 g/l (or less than a 30% perioperative drop), the outcomes are not different. Given the size of our analysis and the large confidence intervals, we cannot rule out the possibility of a cardioprotective effect. In addition, the past demonstrations of cardioprotective effects were predominately seen in the high risk patient population[22] and/or vascular patients.[23–25] Readers should also be aware that more than 40% of the patients in the POISE study[4] had vascular surgery and was the only subgroup found to have a statistically significant reduction in the primary endpoint (see also fig. 3 of POISE[4]). Therefore, our analysis was probably underpowered to show a cardioprotective effect because vascular surgery represented just 9% of the study cohort, and the composite cardiac risk profile was a much lower risk profile (90% of the patients in our matched cohort had a Revised Cardiac Risk Index of 0 or 1). Further to this line of reasoning, our analysis did not prospectively measure troponin in all patients, and it is possible that we have missed some asymptomatic events. This is particularly a risk given that there were

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more troponin measurements in the β-blocked group. We investigated this potential bias in two ways. First, we have investigated the act of measuring a troponin and found that the majority of measurements are negative, but a negative troponin was associated with increased mortality compared with patients who did not have troponin measured (fig. 2), suggesting the act of measuring a troponin is associated with a clinical event or intuition and represents an outcome in that sense. We also conducted a *post hoc* sensitivity analysis to investigate this result. By using propensity matching, as in the primary analysis, we balanced the measurement of troponin in both cohorts, and thus, we feel that the chance of detecting an MI was equal. This analysis continued to show that the rate of MI was twice as high in anemic β-blocked patients. We remain fully cognizant that measurement of troponin is a major limitation.

The POISE study found an association between major blood loss, hypotension, and adverse outcomes. We would suggest that blood loss is a surrogate measure for nadir hemoglobin and/or inadequate fluid therapy, and our analysis similarly shows that blood loss with inadequate replacement is associated with adverse outcomes as well. The amount of blood loss, nadir hemoglobin, and fluids were unmeasured in POISE, and thus, making a comparison of these aspects with our study is impossible. However, because transfusion triggers are variable, POISE was conducted in more than 300 hospitals, and we report a single-institution report, the increased MI rate that we show, compared with that in POISE, is due to more patients with lower nadir hemoglobin in our population. We reiterate that our primary goal was to show an interaction between lowest hemoglobin and β-blocker use.

The relationship we describe between hemodilution and increased ischemic outcomes, in patients receiving β-blockers, was not identified in previous prospective studies.[26,27] Our investigation differed from these in several important areas. First, previous investigations were conducted in cardiac surgery. Second, the sample size was small, 110 patients in total, limiting the ability to detect a difference. Finally, and probably most important, the degree of hemodilution was limited to 100 g/l—a level that our results suggest as safe in noncardiac surgical patients with risks for coronary disease.

Limitations

There are several limitations to be considered when interpreting our study. First, as this was a retrospective observational study, causality could not be determined. It is therefore possible that nadir hemoglobin and β-blockers were associated with adverse outcomes simply because it is a marker for severity of the surgery; *i.e.*, more blood loss in sicker patients would lead to worse outcomes. Second, the effects of unknown or unmeasured confounders on the observed association cannot be ruled out. A case in point is the measurement of troponin, which we speculate is independently associated with clinical acumen; it "feels" like there is something wrong and so we should rule out a cardiac cause. This conjecture is born out by the finding that merely measuring troponin (and getting a negative result), compared with patients who did not have a measurement, is associated with increased mortality at 30 days. Furthermore, we have demonstrated that patients with nadir hemoglobin less than 90 g/l have troponin measured two times more frequently than those with higher nadirs. The data on β-blockers is also a limitation. We have no preoperative data and there could be patients who were withdrawn from β-blockers. These patients would then be assigned to the control arm. Withdrawal of β-blockers has been associated with increased cardiac events.[28] Potentially, this would spuriously elevate the event rate in the control arm. We do not believe this to be a major problem however as we have just completed a prospective analysis of the neurocognitive effects of β-blockers in vascular surgery patients. We found that the incidence of β-blocker withdrawal in this population, in our institution, to be less than 1%.[29] Next, we constructed the preoperative risk profile using International Classification of Disease 10 data, which was collected retrospectively, International Classification of Disease codes lack the sensitivity of prospectively collected data and therefore it is possible that some of our risk calculations are inaccurate as well.[30] Although we have gone to great length to balance known confounders, there may be unknown factors that we have not accounted for owing to the breadth of the variables we have included in our multivariable analyses and to the robustness of our results, which shows similar results in two separate sensitivity analyses, and we believe that the impact of any such error or unknown or unmeasured confounders is likely to be small. Finally, we should caution that this analysis, although it had over 4,000 patients and over 1,000 patients taking β-blockers, it was severely underpowered (which makes it impossible for this analysis to comment on perioperative stroke). Because there are not enough individual events in each category, we were forced to use a composite outcome to increase the power of the analysis. The findings of this study needs to be verified both across institutions and prospectively.

Conclusion

This investigation details the relationship between the degree of hemodilution and ischemic outcomes, in a population of relatively low risk patients with and without β-blockade. We have shown that acute surgical anemia, a reduction of 35% from baseline, increased the risk of cardiac outcomes. This relationship is much worse in β-blocked patients. These findings suggest that the transfusion triggers should be higher for elective surgical patients on β-blockers. Owing to the relatively low risk of our population, we are unable to extend these finding to higher risk β-blocked patients who have been shown in the past to have reduced cardiac outcomes.

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