PCRC Proposal Cover Sheet

Title of Study or Project: Do perioperative beta blockers and blood transfusion therapies modify the effectiveness of the other therapy?

Primary Institution: University of Michigan, Ann Arbor, MI

Principle Investigator: Milo Engoren
Co-Investigators: Sachin Kheterpal, others
Statistician: Elizabeth Jewell

Type of Study: Retrospective Observational

IRB Number/Status:

Hypothesis: That there is a hemoglobin threshold above which beta blockers are protective and below which beta blockers are harmful and that this threshold is modified by RBC transfusion.

Number of Patients/Participants:
Depending on center participation we anticipate tens of thousands to be included in this study.

Power Analysis: Post-Hoc analyses will be conducted. With potentially hundreds of thousands of cases the probability of being underpowered or having high alpha-error is extremely low.

Proposed statistical test/analysis:
Summary and descriptive statistics; Fisher's exact test, Chi square test, student t test or Wilcoxon Rank Sum test; conditional logistic regression, multivariable hierarchical models

Resources (Brief summary of resources for data collection, personnel, financial):
The Multicenter Perioperative Outcomes Group

Do perioperative beta blockers and blood transfusion therapies modify the effectiveness of the other therapy?

Authors: Milo Engoren, Sachin Kheterpal, others

Statistician: Elizabeth Jewell

Resources: MPOG, Department of Anesthesiology

Introduction

Stress related increases in catecholamines during and after surgery increase myocardial oxygen demand via increases in blood pressure and heart rate. In hearts with limited compensatory mechanisms to concomitantly increase myocardial oxygen delivery, such as in patients with coronary artery disease, increases in myocardial oxygen demand may lead to myocardial ischemia, myocardial infarct, heart failure, or death. Beta blockers by lowering heart rate and blood pressure decrease myocardial work and oxygen demand and additionally, by prolonging diastole, increase myocardial oxygen delivery and thus improve the myocardial oxygen supply demand ratio and, clinically importantly, decrease the chances of myocardial ischemia and infarction. In non-surgical patients with coronary artery disease, beta blocker are used to prevent myocardial infarction and when myocardial infarction occurs, beta blocker use decreases infarct size and improves survival.[pasty,peter,herlitz] Early studies in transferring this knowledge to the perioperative setting showed that beta blockers were associated with lower risks of myocardial ischemia and death.[stone, Magnusson, Cucchiara, Mangano] However, more recent studies failed to find this salubrious association. Some even found that beta blockers increased the risks of death.[Poise, Bangalore] While there are methodological differences that may explain the contradictory associations found in the different studies another explanation may lie in another change in anesthesia practice.

For decades, anesthesiologists traditionally followed the 10/30 rule: transfuse to keep the hemoglobin > 10 g/dL or the hematocrit > 30% to maintain oxygen delivery.[adams, kowalyshyn] As some, but not all, recent studies have found an association between perioperative RBC transfusion and worse short and long-term outcomes [Engoren,Koch,karkouti,hajjar, carson, habib] and that the physiologic response to anemia is increased cardiac output to maintain oxygen delivery, anesthesiologists began to defer RBC transfusion until lower hemoglobin values occurred.[Frank] However, the safety of lower perioperative hemoglobin levels may not be generalizable to all patient populations. Two studies, one prospective randomized and one retrospective observational, have suggested that restrictive hemoglobin transfusion triggers were associated with worse outcomes in patients with unstable angina or acute myocardial infarction.[Hebert, Wu] A study of surgical patients who refused blood transfusions for religious reasons found that patients with cardiovascular disease were less tolerant of profound anemia.[carson]

A unifying concept to explain the benefit of beta blockers in the earlier studies and the harm in latter studies may be that perioperative beta blockers are beneficial at higher hemoglobin levels even if these higher levels are achieved by RBC transfusion but that at lower hemoglobin levels they limit myocardial oxygen supply more than they limit myocardial oxygen demand, thus leading to myocardial ischemia that can be prevented by RBC transfusions.

The purpose of this study is to determine the associations between beta blockers, RBC transfusions, and outcomes. Specifically, is there a hemoglobin threshold above which beta

blockers are protective, below which beta blockers are harmful and is this threshold modified by RBC transfusion?

Methods

This is a retrospective, observational cohort study using the Multicenter Perioperative Outcomes Group (MPOG) database which is a limited dataset and conducted with Institutional Review Board (IRB) Approval with waiver of written informed consent. The following MPOG sites will be able to contribute data for this project: University of Michigan, Oregon Health Sciences University, University of Colorado, University of Tennessee, University of Oklahoma, Utrecht, and University of Vermont. Within the MPOG dataset, four high risk procedures will be selected based on their CPT code (pro fee), discharge ICD-9 codes, and/or free text procedure name search. The four procedures of interest are: major vascular surgery (excluding suprarenal aortic clamping, stents, fistulas, below knee or more distal amputations, endovascular AAA stents, and trauma) that was done on an in-patient basis, colorectal surgery of partial or total colectomies, hip fracture, and hip replacement. These procedures were chosen as procedures that frequently are done in patients with cardiovascular morbidities and beta blocker use, associated with perioperative transfusions, and associated with postoperative complications.

For each patient within each surgical procedure we will query information regarding the patient's preoperative beta-blocker use within 24 hours of the operation using SCIP-CARD documentation at each participating site. If the hospital currently does not participate in SCIP-Card we will query the institutions preoperative medications for the documentation of beta-blockers. There is a known limitation that we cannot confirm that the beta-blocker was taken the

day of surgery. In addition, the following co-morbidities will also be queried: hypertension, previous myocardial infarction, coronary artery disease, congestive heart failure, COPD, diabetes, and cerebrovascular accident in addition to basic patient demographics and anthropometric measurements. For intraoperative management, we will query for the anesthetic technique used, the use of intraoperative beta-blockade, and the amount of RBC transfused.

There will be three adverse outcomes that will be investigated for each of the four surgical procedures: hospital death, acute kidney injury (AKI), and myocardial injury. Hospital death will be captured by each site after 2012 and reported directly into the MPOG centralized database. AKI will be defined by KDIGO creatinine criteria (increase $\geq$ 50% or $\geq$ 0.3 mg/dL within the first 3 postoperative days compared to last preoperative value). Myocardial injury will be defined using each hospital's criteria for elevated troponin or CK-MB.

We will exclude patients if they are transfused without having an intraoperative hemoglobin determination. In nontransfused patients, if an intraoperative hemoglobin concentration is not measured, we will use the first postoperative level. If none was obtained within 24 hours postoperatively, the patient will be excluded.

Statistical Analysis

For each of the three outcomes, categorical factors will be analyzed with Fisher's exact test or Chi square test and continuous variables with student t test or Wilcoxon Rank Sum test as appropriate (Table 1). Interaction terms for beta blocker and intraoperative blood transfusion will be created. Two-level multivariable hierarchical models will be developed for each of the

three outcomes in each of the four surgical procedures on interest. Patient co-morbidities will be modeled as fixed effects and each MPOG site will be modeled as the random effect. The fixed effects will be reported as adjusted odds ratios with 95% confidence intervals. The variance of the random effect (center) will be used to calculate the median odds ratio (MOR). The MOR will quantify the extent of variation in each individual outcome explained by the center. A p-value of <0.05 will be considered statistically significant.

Next, to determine if there is a different transfusion threshold between beta blocked and non-beta blocked patients stratified by known CAD or MI history, hemoglobin concentrations will be categorized into 0.5 g/dL ranges and entered into conditional logistic regression models. The lowest intraoperative hemoglobin if the patient was transfused will be used or the first hemoglobin within 24 hours after surgery will be used in the patient was not transfused. [If there are insufficient numbers in each hemoglobin range, the ranges will be combined into bigger ranges.] The four sets of odds ratios (with 95% confidence intervals) for each of the complications will be compared graphically and compared with ANOVA.(Fig 1) Finally, if there is sufficient number of subjects, the analyses will be repeated by type of beta blocker (B selective v. non-B selective) and by name of beta blocker.

MPOG – Perioperative beta-blockers and blood transfusion therapies

PI: Milo Engoren

Specific data columns required for analysis

MPOG Sites to Include: Michigan, Oregon Health Sciences University, University of Colorado, University of Tennessee, University of Oklahoma, Vanderbilt, Utrecht, and University of Vermont – Please include MPOG site ID identifier as well

Standardized Views Requested

1. General Case Information
2. ASA Class
3. Patient Anthropometrics
4. Patient Demographics
5. Anesthesia Technique
6. Case Times

Source	Data Column	Data type	MPOG source table, column, and MPOG concept ID
AIMS (operative info)	Primary surgery CPT code	Character	Aims_billing_header.primary_surgery_cpt
	Primary anesthesia	Character	Aims_billing_header.aims_anesthesia_cpt

	base CPT		
AIMS (H&P)			
	Preop_beta_blocker	Character	AIMS_Preop, MPOG Concept ID 70075
	Hypertension	Character	AIMS_Preop, MPOG Concept ID 70031
	Previous myocardial infarction	Character	AIMS_Preop, MPOG Concept ID 70033
	Coronary artery disease	Character	AIMS_Preop, MPOG Concept ID 70027
	Congestive heart failure	Character	AIMS_Preop, MPOG Concept ID 70026
	Cardiac - other	Character	AIMS_Preop, MPOG Concept ID 70034
	COPD	Character	AIMS_Preop, MPOG Concept ID 70115
	Diabetes	Character	AIMS_Preop, MPOG Concept ID 70046
	Neuro sign/sx	Character	AIMS_Preop, MPOG Concept ID 70094

	Neuro - other	Character	AIMS_Preop, MPOG Concept ID 70090
Laboratory data	Most recent preoperative creatinine value prior to patient in room time for operation	Numeric, 0 – 50	AIMS_LabValues, MPOG Concept ID 5002
	Peak postoperative creatinine value within 7 days of patient out of room time	Numeric, 0 – 50	AIMS_LabValues, MPOG Concept ID 5002
	Nadir postoperative creatinine value within 7 and 30	Numeric, 0 – 50	AIMS_LabValues, MPOG Concept ID 5002

	days of patient out of room time		
	Most recent preoperative hemoglobin prior to day of surgery	Numeric	AIMS_LabValues, MPOG Concept ID 5005
	Nadir Intraoperative hemoglobin value	Numeric	AIMS_Lab Values, MPOG Concept ID 5005 of 5080 or 5081 between the timestamps of Patient in room (MPOG Concept ID 50003) to Patient out of room (MPOG Concept ID 50008)
	First postoperative hemoglobin value	Numeric	AIMS_Lab Values, MPOG Concept ID 5005 of 5080 or 5081 after timesheet for Patient out of room (MPOG Concept ID 50008)
	Nadir postoperative hemoglobin value	Numeric	AIMS_Lab Values, MPOG Concept ID 5005 of 5080 or 5081 after timesheet for Patient out of room (MPOG Concept ID 50008)
Intraoperative Meds			
	Intraop_Metropolol	Numeric	Intraoperative Medications, MPOG Concept ID 10298. Just report if they

			received it at all (yes=1) or did not receive it (no=0)
	Intraop_Atenolol	Numeric	Intraoperative Medications, MPOG Concept ID 10042. Just report if they received it at all (yes=1) or did not receive it (no=0)
	Intraop_Propranolol	Numeric	Intraoperative Medications, MPOG Concept ID 10379. Just report if they received it at all (yes=1) or did not receive it (no=0)
	Intraop_Acebutolol	Numeric	Intraoperative Medications, MPOG Concept ID 10006. Just report if they received it at all (yes=1) or did not receive it (no=0)
	Intraop_Bisoprolol	Numeric	Intraoperative Medications, MPOG Concept ID 10062. Just report if they received it at all (yes=1) or did not receive it (no=0)
	Intraop_Esmolol	Numeric	Intraoperative Medications, MPOG Concept ID 10180. Just report if they received it at all (yes=1) or did not receive it (no=0)
	Intraop_Labetalol	Numeric	Intraoperative Medications, MPOG Concept ID 10242. Just report if they received it at all (yes=1) or did not receive it (no=0)
	Intraop_Pindolol	Numeric	Intraoperative Medications, MPOG Concept ID 10362. Just report if they received it at all (yes=1) or did not receive it (no=0)

	Intraop_Sotalol	Numeric	Intraoperative Medications, MPOG Concept ID 10412. Just report if they received it at all (yes=1) or did not receive it (no=0)
	Intraop_Timolol	Numeric	Intraoperative Medications, MPOG Concept ID 10431. Just report if they received it at all (yes=1) or did not receive it (no=0)
Death master index	Date of death if match in social security death master file based upon SSN & soundex (last name)	Date	Need to know if the patient died during the hospital stay

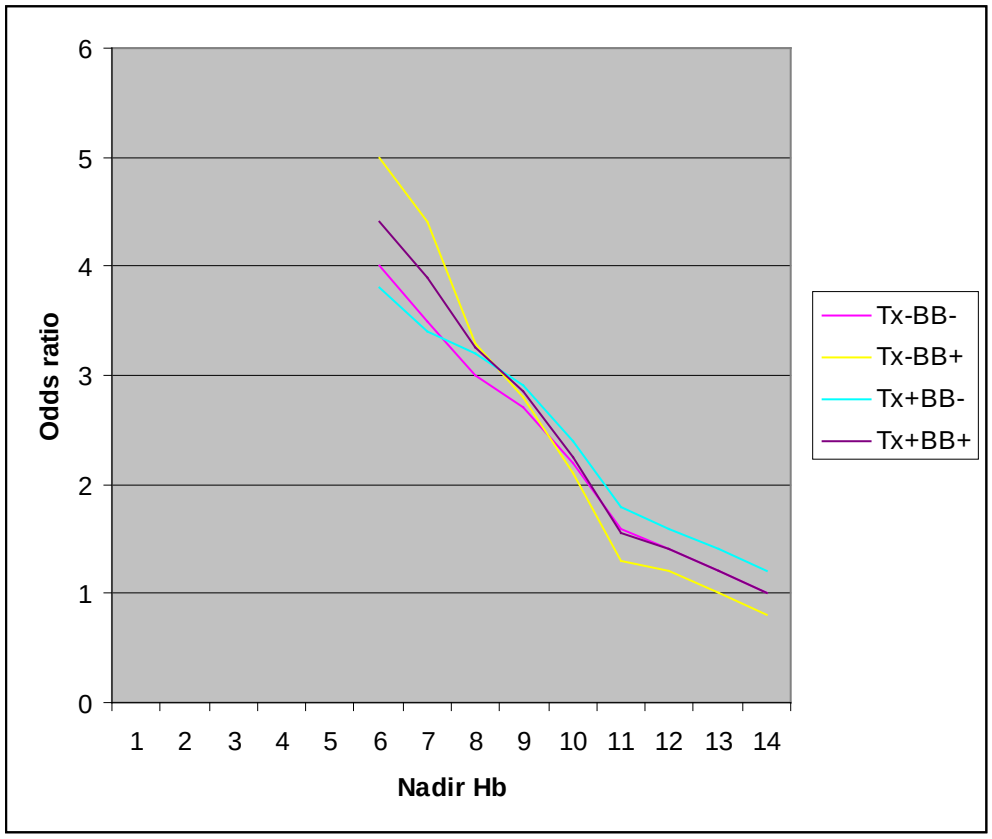

Fig 1 (illustration only. Not from real data.) showing that compared to non-transfused, non-beta blocked patients (Tx-BB-, fuchsia), non-transfused, beta-blocked patients (Tx-BB+, yellow) did worse for Hb < 8, but did better with Hb>8. Patients who were transfused but not beta blocked (Tx+BB-, turquoise) did better for Hb<8, worse for Hb >8 compared to non-transfused, non-beta blocked patients (Tx-BB-, fuchsia). Patients who were transfused and beta-blocked (Tx-BB+, purple) did worse than non-transfused, beta-blocked patients (Tx-BB+, yellow) for Hb<9, but better for Hb>9.

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MPOG Element	MPOG Source