Title: Effects of microplegia on transfusion rates after cardiac surgery: A randomized prospective analysis

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Project Title	Effects of microplegia on transfusion rates after cardiac surgery: A randomized prospective analysis
Short Title	Microplegia Study
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Protocol Amendment 1.1

1. Section 6.0, Table 1: Added and removed variables

Protocol Amendment 1.2

1. Section 6.0, Table 1: Variables moved to Appendix 3
2. Appendix 3: added variables

Protocol Amendment 1.3

1. Change inclusion/exclusion criteria and study design to be more flexible and accurately capture cardiac surgery patient population.

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1.0 INTRODUCTION AND BACKGROUND

Cardioplegia was first introduced as a method to protect the heart during cardiac surgery in the 1950s (1). Initially, it consisted of a crystalloid solution and in the 1970s Follette and colleagues proposed that blood was the best mode of delivery of cardioplegia as it is rich in nutrients and oxygen (2). Blood has better osmotic, buffering, and antioxidant qualities that are needed by ischemic myocardium. More recent studies comparing blood and crystalloid cardioplegias showed that there was less cardiac edema, and recovery of ventricular function was more rapid with blood based cardioplegia (3). A meta-analysis of over 5000 patients corroborated these findings and showed that blood based cardioplegia reduced the incidence of postoperative low cardiac output syndrome and was associated with less myocardial damage (4).

Standard diluted blood cardioplegia can also be modified to undiluted blood cardioplegia also known as microplegia. To compare the cardioprotection of 4:1 blood:crystalloid cardioplegia to microplegia, McCann et al randomized 20 pigs to either group. Cardiac edema was measured using histologic morphometrics and echocardiogram. It was noted that both edema percentage and left ventricular mass were significantly more decreased in the microplegia group. Furthermore, all animals receiving microplegia were successfully weaned off cardiopulmonary bypass, whereas only 40% of those receiving standard cardioplegia were successfully weaned (5).

More recently, Algarni *et al.* showed decreased prevalence of low cardiac output syndrome in patients who received microplegia (n=2,630) (6). Another study compared microplegia and standard cardioplegia in patients undergoing coronary artery bypass grafting and found that the microplegia group had lower troponin levels during the post-operative course. Moreover, microplegia resulted in lower transfusion rates and decreased length of hospital stay (7).

A high rate of patients undergoing cardiac surgery require red blood cell transfusions (RBC). Red blood cell transfusions are strongly associated with both infection and ischemic postoperative morbidity, length of stay, increased early and late mortality, and overall hospital costs (8). Given that previous studies have shown that microplegia is associated with less transfusions, it would be reasonable to incorporate this into practice at Washington University.

2.0 HYPOTHESIS AND AIMS

The hypothesis is that diluted 4:1 cardioplegia used in adult cardiac surgery at Washington University in St. Louis contributes to increased transfusion rates peri-operatively and incorporation of Quest, Inc. microplegia may decrease RBC transfusion rates, and thus, impact overall morbidity and mortality after cardiac surgery.

Specific aims are:
1. To determine if use of microplegia results in less peri-operative transfusions compared to diluted 4:1 cardioplegia.

2. To investigate the effects of microplegia on overall morbidity and mortality during the peri-operative period. We will assess operative mortality and 30 day mortality. We will examine intra-operative and post-operative complications. A complete list of variables to be examined can be found in table 1. We will determine if microplegia results in better myocardial protection than standard cardioplegia by assessing pre-operative, intra-operative and post-operative serum troponin levels.

3.0 INCLUSION CRITERIA

Patients must meet all of the following criteria to be considered eligible for study participation:

1. Are to undergo non-emergent cardiac surgery

2. ≥ 18 years of age.

3. Willing and able to provide informed consent.

4.0 EXCLUSION CRITERIA

Patients must not meet any of the following criteria to be considered eligible for study participation:

1. History of endocarditis.
2. Dialysis-dependent renal failure.
3. Currently on pre-operative mechanical circulatory support (i.e. ECMO, LVAD or intra-aortic balloon pump [IABP]).
4. Contraindication to receiving a blood transfusion (i.e. Jehovah's Witness).

5. Emergent procedures.

5.0 STUDY DESIGN

The hypothesis will be accomplished in a randomized, blinded, prospective institutional study conducted at two sites, Barnes Jewish Hospital and Christian Northeast Hospital. 314 patients will be randomized to either receive diluted 4:1 cardioplegia or nondiluted microplegia. This will be a blinded study to both the patient and surgeon. The patient will be randomized during the preoperative period. Quest Medical Inc. will supply us with the microplegia MPS-2 machines needed to conduct this study. Outcomes will be measured by a blinded clinician.

Microplegia

The microplegia machine to be used for all study subjects is the FDA approved MPS2 Microplegia delivery machine manufactured and distributed by Quest Medical, Inc.

The microplegia solution that is standard of care for all cardiac surgery patients, and which all study subjects will receive is:
Induction
240 mL Baxter Cardioplegia Solution
10. 5 mL Potassium Chloride 2 meq/ml (21 meq)
250.5 mL total volume

Maintenance
747 mL Baxter Cardioplegia Solution
3.4 mL Potassium Chloride 2 meq/ml (6.75 meq)
750.4 mL total volume

Subjects will be randomly assigned to 4:1 cardioplegia or nondiluted microplegia.
4:1 cardioplegia consists of 4 parts crystalloid intravenous fluid to one part human blood.
Nondiluted microplegia consists of all parts human blood.

Recruitment
Potential participants will be identified as inpatients or in new patient clinics of the adult cardiac surgeons in the Division of Cardiothoracic Surgery, Department of Surgery, Washington University School of Medicine. Patients will be introduced to the study at the preoperative consultation visit, at which point they will be invited to participate and provide informed consent if they agree to join the study. Potential subjects will have at least 48 hours, typically longer and up until the time of surgery to consider participation and may take the consent home to discuss with friends and family, if they so choose. They will have ample time to ask questions of the surgeon prior to agreeing to participate. Upon providing informed consent, the subject will be considered enrolled into the study.

Peri-operative period
Troponins will be drawn in the operating room prior to initiation of cardiac surgery and post-operatively upon arrival to the ICU, 12 hours, and 24 hours.

Subjects will undergo their standard of care, planned cardiac surgery procedure as directed by their treating surgeon.

Given that our primary endpoint is transfusion requirement, we will assess this need throughout the entire peri-operative period. Standard blood draws after surgery to evaluate hematocrit will be used for analysis. We will use the electronic medical records to obtain this information.

Post-Operative Follow-Up
There is no active participation for subjects beyond the 24 hour troponin and hematocrit collection time points. Health information on post-operative complications, should they occur, will be collected until the patient is discharged from the hospital. Data on vital status will be collected from the subject's medical record at the time of the standard of care 30-day post-operative visit with the surgeon.

6.0 OUTCOME MEASURES (DATA)

Data will be obtained from the electronic medical record system at Washington University. Study staff from each participating site will review the subject's medical record and obtain the study-specific data to include but is not limited to the following. For a complete list of all data variables to be collected please see table 1. The study-specific data will be collected by the study staff and entered into a REDCap database that will be created specifically for this study. REDCap is a mature, secure web application for building and maintaining databases (https://redcap.wustl.edu).

Electronic study data will be entered in a secure REDCap database. Only investigators and the study team for this study will have access to the study data. They will each use a unique log-in ID and password that will be kept confidential.

See Appendix 3: Data Collection for Table 1

7.0 RISKS

All microplegia will be delivered using the MPS-2 Myocardial Protection System. This is an approved device currently used in many cardiac centers worldwide. There is no change in risk that can be associated with the use of microplegia versus standard cardioplegia currently used as standard of care.

Blood drawing poses the following risks: pain, bleeding, or bruising and rarely, infection. All peri-operative blood draws can be performed while the subject has a standard of care intravenous line in place. There will be no needle sticks required.

There is a rare risk of breach of confidentiality of study data.

8.0 BENEFITS

There are no known direct benefits to subjects; however, there will be an improved understanding of cardioplegia techniques and possibly improved outcomes of cardiac surgery patients.

9.0 STATISTICAL ANALYSIS

Continuous variables will be expressed as mean ± standard deviation or as median with range. Categorical variables will be expressed as frequencies and percentages with outcomes compared using the χ^2 or the Fisher exact test. Continuous outcomes will be compared using the *t* test for means of normally distributed continuous variables and the Mann-Whitney U nonparametric test for skewed distributions. Significant covariates on univariate analysis ($p \leq 0.10$) or covariates deemed clinically relevant based on experience will be entered into a multivariate binary logistic regression analysis.

A sample size of 314 patients will be randomized to either receive standard 4:1 cardioplegia or microplegia. The sample size was calculated based on a one tailed test with alpha 0.05 and beta 0.2 (80% power) to detect a 25% relative risk reduction in pRBC units transfused. An interim analysis will be completed following the enrollment of 150 patients.

10.0 DATA AND SAFETY MONITORING

The PI and sub-I, Dr. Schuessler, will monitor the study for any serious adverse events (SAEs). All serious adverse events will be reported to the Washington University Human Research Protection Office per their guidelines and policies by the research coordinator(s). An investigation into the event will be conducted, and a findings reported.

11.0 REFERENCES

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12.0 ABBREVIATIONS AND ACRONYMS

COPD	Chronic obstructive pulmonary disease
CPB	Cardiopulmonary bypass
FFP	Fresh frozen plasma
ICU	Intensive Care Unit
LVEF	Left ventricular ejection fraction
OR	Operating room
PCI	Percutaneous coronary intervention
pRBC	Packed red blood cells
WMSI	Wall motion score index

13.0 APPENDIX 1: Protocol for transfusion of packed red blood cells (pRBC)

- Please record blood transfusion on the peri-operative blood transfusion form. Deviations should be justified clearly on the peri-operative transfusion form.
- Discussion with primary cardiac surgeon or fellow/resident should occur prior to transfusion whenever possible.

Intraoperative:

1. It is appropriate to transfuse if predicted hematocrit on cardiopulmonary bypass <20% or actual hematocrit on cardiopulmonary bypass falls below 20%.

Postoperative:

1. It is appropriate to transfuse if hemoglobin falls below 7 g/dL

2. It is appropriate to transfuse if hemoglobin falls below 8 g/dL and any of the following are present:

-patient has borderline hemodynamics, or has become dependent upon pressors/inotropes

-patient is symptomatic (i.e. dizziness, lightheadedness, unable to ambulate)

-patient is in acute renal failure

3. It is appropriate to transfuse in any case of ongoing hemorrhage/acute blood loss

14.0 APPENDIX 2: TRANSFUSION FORMS

INTRAOPERATIVE TRANSFUSION FORM

*Study number*_____ *Date of Surgery* _____

INSTRUCTIONS

1. All blood (pRBC) transfusions will be recorded on the transfusion form.

2. Deviations from the protocol must be justified clearly on the transfusion form.

PROTOCOL

It is appropriate to transfuse:

- if predicted hematocrit on cardiopulmonary bypass <20%
- or actual hematocrit on cardiopulmonary bypass falls below 20%

1st Transfusion				
Date	**# of units**	**Ordered by (name)**	**Predicted/Actual Hematocrit (%)**	**Justify if Hematocrit > 20%**

2nd Transfusion				
Date	**# of units**	**Ordered by (name)**	**Predicted/Actual Hematocrit (%)**	**Justify if Hematocrit > 20%**

3rd Transfusion				
Date	**# of units**	**Ordered by (name)**	**Predicted/Actual Hematocrit (%)**	**Justify if Hematocrit > 20%**

4th Transfusion				
Date	**# of units**	**Ordered by (name)**	**Predicted/Actual Hematocrit (%)**	**Justify if Hematocrit > 20%**

Transfusion *(example)*				
Date	**# of units**	**Ordered by (name)**	**Predicted/Actual Hematocrit (%)**	**Justify if Hematocrit > 20%**
Aug 8, 2018	*2*	*Dr. First Last*	*25*	*Active bleeding*

POSTOPERATIVE TRANSFUSION FORM

*Study number*_____ *Date of Surgery* _____

INSTRUCTIONS

1. All blood (pRBC) transfusions will be recorded on the transfusion form.

2. Deviations from the protocol must be justified clearly on the transfusion form.

PROTOCOL

1. It is appropriate to transfuse if hemoglobin falls below 7 g/dL
2. It is appropriate to transfuse if hemoglobin falls below 8 g/dL and any of the following are present:
    - patient has borderline hemodynamics, dependent upon pressors
    - patient is symptomatic (i.e. dizziness, lightheadedness, pallor, shortness of breath)
    - patient is in acute or chronic renal failure
3. It is appropriate to transfuse in any case of ongoing hemorrhage

1st Transfusion				
Date	**# of units**	**Ordered by (name)**	**Hgb level (g/dL)**	**Justify if Hgb ≥7.0 g/dL**

2nd Transfusion				
Date	**# of units**	**Ordered by (name)**	**Hgb level (g/dL)**	**Justify if Hgb ≥7.0 g/dL**

More on other side if needed

3rd Transfusion				
Date	**# of units**	**Ordered by (name)**	**Hgb level (g/dL)**	**Justify if Hgb ≥7.0 g/dL**

4th Transfusion				
Date	**# of units**	**Ordered by (name)**	**Hgb level (g/dL)**	**Justify if Hgb ≥7.0 g/dL**

Transfusion *(example)*				
Date	**# of units**	**Ordered by (name)**	**Hgb level (g/dL)**	**Justify if Hgb ≥7.0 g/dL**
Aug 8, 2018	*2*	*Dr. First Last*	*7.6*	*Borderline hemodynamics, dependent upon pressors*

15.0 Appendix 3: Data Collection

Table 1: Baseline pre-operative, operative, and post-operative variables to be examined.

Pre-operative variables	**Intra-Operative Variables**	**Post-Operative Variables**
Age	pRBC transfusion (see appendix 2, peri-operative transfusion form): date, number of units, name of staff ordering transfusion, actual/predicted hematocrit, justification if hematocrit >20%	pRBC transfusion (see appendix 2, perioperative transfusion form): date, number of units, name of staff ordering transfusion, hemoglobin level, justification if hemoglobin ≥7.0 g/dL.
Weight	Platelet transfusion: number of units	Platelet transfusion: number of units
Dyslipidemia	FFP transfusion: number of units	FFP transfusion: number of units
Hypertension	Mortality	Hematocrit on arrival to ICU
~~COPD~~	~~Clamp time~~	Hematocrit 24 hours post-operatively
Coronary artery disease	Amount of cardioplegia/microplegia delivered	30 day mortality
Liver disease	Type of surgery	Time on ventilator
Cerebrovascular disease	CPB time	Hours in the intensive care unit
Previous cardiac interventions	Cross-clamp time	Length of hospital stay
History of arrhythmia	~~Cardioplegia technique~~	Renal failure
Diabetes mellitus	Number of grafts	Pulmonary complications
LVEF (%)	Concomitant procedures	Low output syndrome
Congestive heart failure	Pre-CPB hematocrit	Myocardial infarction
Peripheral vascular disease	On-CPB hematocrit	Serial troponins: arrival to ICU, 12 and 24 hours post-op
Hemoglobin, hematocrit	Post-CPB hematocrit	New onset post-op atrial fibrillation
Creatinine	Date of surgery	Stroke
Troponin	Skin incision to skin close time	Mortality
Previous PCI +/- stents	Cardioplegia Delivery	Readmission
Angina	Additive Volume	Readmission date
BMI	Arrest Agent Volume	Readmission reason
Height	Total CDPG	
Ethnicity	Crystalloid Amount	
Race	Crystalloid Total	
Chronic Lung Disease	Anesthesiologist	
Immunocompromise	Perfusionist	
Mediastinal Radiation	Starting glucose	

Thoracic Aorta Disease	Final glucose	
Sex	TEE score	
Date of admission	Time to arrest	
	Volume to arrest	
	Cryoprecipitate volume	Cryoprecipitate volume