

Lactated Ringers versus 5%
Human Albumin: A Double-
Blinded, Randomized,
Prospective Study in Cardiac
Surgical Patients

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**Lactated Ringer's versus 5% Human Albumin:
A Double-Blinded, Randomized, Prospective Study in
Cardiac Surgical Patients**

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ABSTRACT

Following IRB approval and written informed patient consent, 40 elective, cardiac surgical patients will be randomized to two different fluid therapy regimens, 5% human albumin only or Lactated Ringer's only, beginning in the intraoperative period and up to 6 hours in the intensive care unit. Providers and patients will be blinded to the fluid administered in the operating room and intensive care unit. The primary outcome measure will be the total volume of 5% human albumin or Lactated Ringer's given during the study period to maintain specified hemodynamic guidelines. Hemodynamic instability will be defined according to each patient's stipulated baseline parameters. Fluid will be administered at the request of providers in the operating room and intensive care unit in compliance with a perioperative fluid algorithm. Outcome measures of hemodynamic instability will include systolic and diastolic blood pressures; mean arterial pressure, central venous pressure, cardiac index, urine output, and vasopressor use. Alveolar-arterial gradient will be assessed between the two choices of fluid to determine any relationship with fluid choice and duration of intubation in the intensive care unit. Blinding of the fluid therapy has not been done in this group of patients so detection of bias towards one of the fluids may be appreciated.

I. SPECIFIC AIMS

Specific Aim 1: To determine the ratio of 5% human albumin to Lactated Ringer's (LR) by examining total fluid volume.

Specific Aim 2: To determine whether or not patients will experience decreased vasopressor and blood product requirements as well as decreased time to extubation and length of intensive care unit (ICU) stay related to less total fluid volume and reduced alveolar-arterial (A-a) gradient.

Specific Aim 3: To determine which fluid, LR or 5% human albumin, is the ideal fluid to administer to cardiac surgical patients in order to maintain individual patient hemodynamic stability without fluid overload.

Specific Aim 4: To determine whether provider bias plays a role in choosing and administering fluid in the operating room (OR) and ICU.

HYPOTHESIS

Hypothesis 1: The individual total fluid volume will be less with 5% human albumin compared to LR in the perioperative cardiac surgical patient.

Hypothesis 2: The A-a gradient with 5% human albumin compared to LR will be lower in the perioperative cardiac surgical patient.

Hypothesis 3: Provider bias largely determines which fluid will be administered to perioperative cardiac surgical patients.

II. BACKGROUND AND SIGNIFICANCE

There has been a great deal of research done on ideal fluid therapy in general populations as well as critically ill patients; however, ideal fluid therapy in the cardiac surgical patient has not been identified. There has been an extensive amount of debate regarding ideal fluid therapy dating back as far as 1977 for both medical and surgical patients.(1) Adequate fluid volume plays a major part in maintaining the necessary hemodynamics to prevent organ damage during cardiac surgery. Cardiopulmonary bypass (CPB) frequently causes an inflammatory response(2) that results in capillary leakage and interstitial edema. Other factors also contribute to a depletion of circulatory volume during surgery including hemorrhage, diuretics, and vasoactive drugs.(3) Fluids such as crystalloid and colloid have traditionally been given to meet volume replacement demands associated with cardiac surgery. Two commonly administered fluids for perioperative volume replacement associated with cardiac surgery are colloids (5% human albumin) and crystalloids (LR).

Cardiac surgery patients initially present with a “shock-like” state shortly after an incision is made called the ebb phase. The ebb phase commences with initial peripheral vasoconstriction, a shifting of blood from the peripheral to major organs, and a reduced body temperature. Shortly after the ebb phase, the flow phase causes an improved cardiac index (CI), vasodilation, pyrexia, and an increase in capillary permeability. Considering the vasodilation and increase in capillary permeability, giving fluid during the flow phase can cause a pooling of fluid in the extravascular space. Destruction to the endothelial glycocalyx layer of the vasculature causes high transcapillary escape rates. Shedding of the endothelial glycocalyx layer seems to occur in cardiac surgery with and without CPB. With this physiology in mind, it would appear that there should be no difference between crystalloids and colloids in maintaining normovolemia.(4) It is

known that the intravascular Starling forces are altered with the initiation of CPB. The increased hydrostatic pressures, generated from left ventricular dysfunction, and the decreased colloid oncotic pressures, resulting from hemodilution, combine to affect intravascular volume. This would suggest that fluid selection might have an impact on extravascular lung water, interstitial edema, and respiratory dysfunction following CPB and during the ICU period.

A-a gradient is a simple but useful clinical measurement⁽⁵⁾ that reflects the degree of ventilation/perfusion mismatch (V/Q).⁽⁶⁾ There is a wide distribution of A-a gradient values. Alveolar gas exchange depends on a slightly unbalanced V/Q but with great capacity to recruit blood to adjust to very strenuous demands and maintain the V/Q so that the A-a gradient remains low.⁽⁷⁾ In 1992, Moore et al. was able to decrease the A-a gradient in patients with congestive heart failure with only minimal oxygen supplementation and their exercise tolerance was significantly improved.⁽⁸⁾

Many different crystalloid solutions are available to treat patients. All of them contain different osmolality and concentrations of electrolytes. Lactated Ringer's is considered a full electrolyte crystalloid that relates highly to the composition of human plasma. Plasma volume is responsible for 4% of total body weight compared to the interstitium that is 16% of total body weight.

Crystalloids are diffused evenly between the intravascular and extravascular spaces, so there is a large difference in the amount of crystalloid needed to maintain intravascular volume compared to colloids (4:1 ratio).⁽³⁾ Considering the amount of crystalloid that may be required to replace blood loss, the patient is at an increased risk for substantial fluid accumulation in the extravascular compartments and fluid overload.⁽³⁾ In contrast, Shaw et al.⁽⁴⁾ has reported only a 30% greater efficacy in boosting intravascular space with colloids compared to crystalloids in a 1:1.2 to 1:1.4 ratio. The uncertainty regarding the amount of crystalloid necessary to replace

ongoing blood loss to maintain effective circulating volume is a drawback for crystalloid resuscitation. Increased fluid in the extravascular space combined with CPB, anesthesia, hypothermia, medications, and transfusions could potentially lead to postoperative pulmonary edema and inadequate gas exchange.(9) A chart review conducted in 2009 of 41 major vascular surgery patients showed that when patients were given less than 3 liters of LR they had a decrease in time of mechanical ventilation and length of ICU stay.(10) Similarly cardiac surgery patients typically will be exposed to more than 3 liters of fluid in a case and in the immediate postoperative period.

Albumin has long been considered the gold standard for volume expansion.(11) It is the most abundant protein in human plasma and accounts for 70% of oncotic pressure. Albumin is synthesized in the liver but is not stored anywhere if it were to be needed quickly.(12) Colloid solutions, in general, have a high molecular weight and leave the intravascular space slowly through capillary walls applying colloid-osmotic pressure and causing fluid to be retained within the intravascular space. Human albumin is also important for transporting calcium, magnesium, and medications.(3) Albumin administration as a volume expander has been criticized for its cost, availability, and the potential for disease transmission since it is obtained from human donors.(13) Some studies have been performed which showed detrimental effects associated with albumin. A well-known study to report adverse results with albumin is the systematic review conducted by the Cochrane Group in 1998. This review analyzed 30 randomized controlled trials. The results suggested a higher mortality rate in critically ill patients with hypoalbuminaemia, burns, and hypovolaemia from trauma or surgery.(14) In response to this review, the 2004 SAFE Trial showed no difference in mortality in critically ill patients when crystalloid and colloid were compared. This study was a significant milestone in treating

critically ill patients and disproving detrimental effects of albumin; however, cardiac surgery patients were excluded from the study.(15)

In 1992, a review article looking back as far as the 1970s, found that colloid solutions were the preferred fluid administered to postoperative cardiac surgical patients.(13) This article noted that colloids, in animal testing, do not readily pass through membranes leading to further volume expansion compared to crystalloids that tend to distribute according to compartment ions. Since sodium is primarily an extracellular cation, normal saline tends to distribute in extracellular compartments. A review of 79 randomized controlled trials in 2003 compared albumin to control regimens of crystalloids, artificial colloids, low-dose albumin, or no albumin.(16) The target indicators were ascites, burns, brain injuries, hypoalbuminaemia, cardiac surgery and non-cardiac surgery. Fourteen of the 79 studies focused on volume expansion in the cardiac surgery patient. Albumin showed more favorable outcomes in these trials maintaining colloid oncotic pressure-pulmonary artery wedge pressure gradients at close to normal levels, less fluid requirements, and more successful hemodilution compared to crystalloids. In 2006 a prospective, blinded, randomized trial, looking at 90 minute filling pressure-guided fluid challenge after cardiac or major vascular surgery, favored albumin as the fluid of choice. Significantly more saline had to be infused in these patients in comparison with albumin. The patients that received albumin had an increase in colloid oncotic pressure as well as heart rate (HR), mean arterial pressure (MAP), CI, central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), global end-diastolic volume index, global ejection fraction, stroke volume index, and left ventricular stroke work.(17)

Since the studies that have been done up to this time have not provided the level of evidence based results concerning optimal fluid therapy for perioperative cardiac surgical patients,

healthcare providers may have developed an unfounded bias towards one fluid type or the other. A questionnaire completed by 270 physicians in Canada revealed that most selected colloids for treatment of oncotic pressure and blood loss. Crystalloids were chosen for their low cost, few side effects, and the belief that crystalloids contain most of what a patient needs.(18) In 1995, 24 medical professionals were asked to participate in developing guidelines for using albumin, nonprotein colloids, and crystalloids based on current literature. The resulting guidelines included 12 indications for fluid administration. The cardiac surgery guidelines made crystalloids the fluid of choice for priming volume of CPB. It also suggested administration of nonprotein colloids used in conjunction with crystalloids if there was a concern for pulmonary edema. Crystalloids were considered first line approach postoperatively, followed by nonprotein colloids, and then albumin.(19) A criticism of this study was the number of healthcare professionals that participated in the study but were not specialists in cardiac surgery. Understanding the motivation of healthcare providers for selection of certain types of resuscitation fluids in cardiac surgery and the ICU could prove beneficial for future research.

In January of 2015, a systematic review and meta-regression analysis of 48 studies related to the selection of crystalloid or colloid for fluid therapy was conducted.(1) Forty-three of the studies were randomized controlled trials. This review found that older studies used albumin in a ratio of 4:1 over crystalloids. However, in cardiac surgery patients, the ratio of albumin was 3:1 over crystalloid. The colloid to crystalloid ratio varied in relation to the decade that the trial was conducted and not according to type and indication for fluid and patient population. There were many different endpoints in the study, but A-a gradient was not included. Overall, this systematic review of Cortes et al.(1) supports the idea of decreased fluid requirements when colloids are used. This study speculated that the reason for a decrease in the ratio between colloids and

crystalloids over the years is that patients are receiving fluid treatment earlier than in the past. Furthermore, this study has shown an increase in albumin levels even if patients are exhibiting capillary permeability issues.

Our study will look at crystalloid compared to albumin in relation to total fluid volume and A-a gradient in the both the intraoperative and postoperative periods. There is only one study(17) that reported the double-blinded administration of fluid after cardiac surgery for only a 90-minute period and noted the physiological changes. The bias associated with fluid administration in the past may adversely affect patient outcomes. Because the study is blinded, stronger recommendations may be formulated giving guidance to healthcare providers and possibly improving patient safety.

III. PRELIMINARY DATA

The investigators of this study have had prior experience performing blinded, randomized, prospective trials in cardiac surgical patients.(20-23) These studies involved successful blinding in difficult clinical situations. The cardiac surgical and ICU personnel have significant experience in the performance of these types of studies that require blinding. Several of the authors on this study are critical care physicians that work with the cardiac patients that will be enrolled.

IV. RESEARCH DESIGN AND METHODS

Sample-Size/Statistical Power Considerations

From previous studies exploring differences in fluid requirements between crystalloids and albumin solutions(1) we anticipate that the distribution of fluid volume will likely be skewed, but

the effect size (difference between groups in SD units) will be at least 1.0. In general, a sample-size of N=40 (N=20 per group) will provide statistical power (two-tailed, alpha=0.05) of greater than 80% to detect a difference between groups of 1 SD. Therefore, a total sample-size of N=40 is proposed.

Data Analysis

The current investigation utilizes a straightforward, randomized design. Unless otherwise specified, analyses will be performed using an intention-to-treat approach whereby subjects are analyzed according to randomized treatment. Data will be summarized using mean \pm SD or median (25th, 75th percentile) for continuous variables and frequency percentages for categorical variables. For the primary analysis, the total volume of study fluid (5% human albumin or LR) administered in the perioperative period and up to 6 hours after ICU admission will be compared between groups using the two-sample t-test or rank sum test. Additional analyses will be performed for secondary endpoints. For these analyses binary endpoints will be compared between groups using the Fisher's exact test and continuous variables will be compared between groups using the two-sample t-test or rank sum test. Model assumptions for each analysis will be validated and transformations or nonparametric methods will be utilized as appropriate. In all cases, two-sided tests will be performed with $p \leq 0.05$ used to denote statistical significance.

Randomization

Subjects will be randomized to one of two study groups using a randomization schedule prepared by the Division of Biostatistics. The randomization schedule will be generated using blocks of size 4 to ensure that after every 4th subject is enrolled an equal number of subjects are assigned to each fluid regimen. Using this randomization schedule, individual randomization cards will be created and placed in sealed envelopes labeled according to a sequentially assigned subject

randomization number. At the time of randomization, a subject will be assigned the next sequential subject randomization number and the corresponding envelope will be opened to determine the treatment assignment.

Patients

Following IRB approval and written informed consent patients having elective cardiac surgery between the ages of 18 and 99 performed by Drs. Schaff and Dearani are eligible. Patients will not be excluded for taking aspirin, heparin, or warfarin preoperatively. Exclusionary criteria include: previous sternotomy, emergency surgery, combined procedures involving vascular or thoracic operations, congenital heart repair, hypothermic CPB < 28°C; serum creatinine ≥ 1.5 mg/dL, dialysis dependent renal failure, any neurologic injury or event within 30 days (including transient ischemic attack), cerebrovascular accident with significant residual neurologic deficit, pre-existing clotting disorder, platelet receptor GPIIb/IIIa antagonists medication received within 48 hours, steroids, severe chronic obstructive pulmonary disease with FEV₁ < 45% of predicted, home oxygen use, previous difficult intubation, acute normovolemic blood conservation techniques, primary liver disease with serum AST > 31 U/L, circulatory arrest, thrombolysis, left ventricular ejection fraction < 40%, intra-aortic balloon pumps, total hearts, ventricular assist devices, ongoing congestive heart failure, pregnant women, and adults lacking capacity to consent. Any patients initially enrolled in the study that end up with an intra-aortic balloon pump, left ventricular assist device, or on extracorporeal membrane oxygenation will be eliminated from the study.

Patients will be maintained on their current preoperative medications until they arrive in the OR. The anesthetic induction will be fentanyl 1-4 mcg/kg, midazolam 0.025-0.05 mg/kg, rocuronium 0.5-0.6 mg/kg and propofol 1-1.5 mg/kg. Anesthetic maintenance will be isoflurane 0.4-1.2%

and fentanyl 2 mcg/kg/hr or sufentanil 0.5 mcg/kg/hr. With chest closure, the patient will be transitioned to propofol 15-50 mcg/kg/min or dexmedetomidine 0.2-0.7 mcg/kg/hr. An arterial catheter will be placed either radially or femorally to identify the blood pressure (BP) continuously and allow for sampling of blood for laboratory tests including arterial blood gases (ABGs). Central venous access and monitoring will be accomplished by the insertion of a pulmonary artery catheter in the internal jugular vein. Standard methods for patients undergoing cardiac surgery requiring CPB will include standard priming solution (crystalloid, mannitol 12.5%), membrane oxygenator, non-pulsatile flow of 2.0-2.4 L/min/m², MAP maintained during CPB between 50 and 90 mmHg, nasopharyngeal temperature between 28°C and 37°C, and conventional ultrafiltration to a volume of 27 ml/kg.(24) Packed red blood cells will be added to the priming volume if the patient's hemoglobin (Hgb) is estimated to be < 8.0 g/dL upon initiation of CPB. Packed red blood cells will also be given if the Hgb falls below 7.5 g/dL at any time during CPB.

Group Designations

Group A will receive LR and group B will receive 5% human albumin as the sole maintenance fluid and volume expander intraoperatively and for the initial 6 hours after admission to the ICU. All patients will be given fluid at the request of the healthcare provider in response to hemodynamic changes with help from the fluid algorithm in Figure 1.

Blinding

All medical personnel caring for the patient will be blinded to the identity of the fluid regimen used in the OR and ICU except for the study personnel administering the fluid. The study staff will have institutional privileges and qualifications to administer fluids. . Funding is currently being pursued for study staff. Albumin, Lactated Ringer's, and IV tubing for each fluid will be

stocked in a cart that can only be accessed by the blinding staff. This cart will be concealed with a room divider from the OR and ICU staff. Intravenous pumps and tubing that contain the designated fluids will be concealed from the patient's medical providers by a large curtain and tubing covers. The blinding will prevent the medical providers (anesthesiologist, nurse anesthetist, surgeon, critical care physician, and nurse) from realizing the type or amount of fluid the patient has received. The healthcare providers will determine the rate and duration of fluid infusions aided by the fluid algorithm in Figure 1 while study personnel carry out the orders. The physicians will not be allowed to compare fluid amounts but only assess physiologic parameters to determine if further volume is required to treat the patient. The blinding may be broken at any time the physician caring for the patient believes it necessary for continuation of care. Blood products will be administered, without blinding, by the providers in the room as needed.

Outcome Measures

Total fluid administered indexed to weight will be the primary outcome measure, and the A-a gradient as a secondary measure will be determined from ABGs obtained after induction of anesthesia, after initiation of CPB, prior to separation of CPB, 10 minutes after protamine, upon admission to the ICU, and with extubation. Other outcome measures will include hemodynamic measurements: BP, MAP, CI, and CVP. Hemodynamic measurements will be obtained at the following times except for CI: sternotomy, post heparinization, 2 min after separation from CPB, 10 min after protamine administration, 5 minutes after sternal closure, and immediately prior to transfer from OR. Hemodynamic measurements will also be obtained at 1 hour, 2 hours, 4 hours, and 6 hours after ICU admission. The CI will be obtained at the following times: 10 min after protamine, 5 min after sternal closure, 10 min after ICU arrival, 2 hours, and 6 hours after admission to the ICU.

Ten minutes after protamine, the hemostatic condition of the surgical field will be classified as dry, moderate, or wet by the surgical and anesthesia staff. Packed red blood cells will be considered for a Hgb < 8.0 g/dL or if ischemia, hypotension, or rapid blood loss necessitate transfusion. Once in the ICU, PRBC cell salvage blood will be administered first before PRBC are given. The triggering hemoglobin is < 8.0 g/dL unless there are mitigating circumstances such as acute coronary ischemia or uncontrolled bleeding. Mediastinal chest tube drainage will be recorded hourly for 6 hours after ICU arrival. Upon arrival to the ICU, all neuromuscular blockade will be reversed. Sedation will be maintained with propofol or dexmedetomidine and a patient controlled analgesia pump will be started with a basal rate of 25 mcg/hr of fentanyl. A standardized, initial ventilator setting and subsequent adjustment and ventilation weaning protocol is instituted for all patients shown in Figure 2. After determining the patient is stable from a hemodynamic and hematologic standpoint and there is no bleeding, the sedation will be weaned and eventually discontinued in conjunction with weaning of mechanical ventilation. The critical care provider, who is blinded to the subject's group designation, is responsible for making the final decision regarding tracheal extubation.

Primary Endpoint

The primary endpoint will be the total fluid volume of 5% human albumin or LR administered in the perioperative period up to 6 hours in the ICU.

Secondary Endpoint

The secondary endpoint will be A-a gradient, which will be assessed with every ABG, in response to the administered volume expanders, 5% human albumin or LR.

Tertiary Endpoint

All providers in the room including the surgeon, anesthesiologist, nurse anesthetist, and nursing staff in the OR and ICU will be asked to fill out a survey on each patient regarding which type of fluid they feel the patient received during the patient's care. The providers will only be able to look at hemodynamic monitoring trends of each patient to determine the type of fluid. They will be asked to provide a reason for choosing that particular fluid and will also be asked to talk to study staff if they feel blinding has been compromised.

V. HUMAN SUBJECTS

Detailed description: Subject Inclusion and Exclusion Criteria

Adult male and non-pregnant female patients undergoing elective cardiac surgery at this facility between the ages of 18 and 99 years of age are eligible. Patients may also be receiving aspirin, heparin, or warfarin preoperatively. Exclusionary criteria include: previous sternotomy, emergency surgery, combined procedures involving vascular or thoracic operations, congenital heart repair, hypothermic CPB $< 28^{\circ}\text{C}$, serum creatinine ≥ 1.5 mg/dL, dialysis dependent renal failure, any neurologic injury or event within 30 days (including transient ischemic attack), cerebrovascular accident with significant residual neurologic deficit, severe chronic obstructive pulmonary disease with $\text{FEV}_1 < 45\%$ of predicted, home oxygen use, previous difficult intubation, acute normovolemic blood conservation techniques, primary liver disease with serum $\text{AST} > 31$ U/L, circulatory arrest, thrombolysis, pre-existing clotting disorder, platelet receptor GPIIb/IIIa antagonists medication received within 48 hours, steroids, left ventricular ejection fraction $< 40\%$, intra-aortic balloon pumps, ongoing congestive heart failure, ventricular assist devices, total hearts, pregnant women, and adults lacking capacity to consent. Any patients

initially enrolled in the study that end up with an intra-aortic balloon pump, left ventricular assist device, or on extracorporeal membrane oxygenation will be eliminated from the study.

Population: We will study 40 elective cardiac surgical patients to be randomized to 2 groups.

Recruitment of patients: Patients will be recruited prior to surgery.

Potential risks: All of the fluids in this study are FDA approved for this purpose. The potential risks of this study are inadequate or excessive fluid administration. The fluid administration will be under the direction of an experienced medical provider that minimizes the risk of over or under infusion of fluid.

Protection: Patient confidentiality will be rigorously maintained by use of secure files and elimination of patient identifiers (beyond a confidential code) on each record or sample. Qualified physicians will perform all invasive procedures for clinical purposes. Additionally, if serious complications occur the individuals will receive care from Mayo Clinic physicians who are experts in treatment of that particular complication. Finally, we will monitor all of our subjects and keep a detailed database of major and minor complications.

Benefits: No direct benefits to the participant.

VI. GENDER/MINORITY MIX

The gender and minority mix will reflect that of the cardiac surgical population.

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