

The Impact of Low Chloride Containing Fluids on Acute Kidney Injury after Cardiopulmonary Bypass as Assayed by Urinary [TIMP2]*[IGFBP7]

PROTOCOL TITLE:

The Impact of Low Chloride Containing Fluids on Acute Kidney Injury after Cardiopulmonary Bypass as Assayed by Urinary [TIMP2]*[IGFBP7]

Brief Title: Fluid Chloride and AKI in Cardiopulmonary Bypass

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REGULATORY FRAMEWORK:

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Is this a clinical trial under ICH-GCP E6? ☒ Yes ☐ No

If yes, please confirm that the research team is familiar with and agrees to comply with the investigator requirements cited in ICH-GCP E6. ☒ Yes ☐ No

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1. Objectives

- 1.1. To determine whether the use of a balanced-salt / physiologic level of Cl⁻ crystalloid solution (Isolyte) as compared to NS in cardiac surgery leads to less kidney injury as measured by the composite [TIMP-2]*[IGFBP7] bioassay.

2. Background

- 2.1. Acute kidney injury (AKI) is a potential complication for patients undergoing cardiac surgery. AKI in post-cardiac surgery patients is associated with adverse outcomes, such as prolonged intensive care and hospital stay, diminished quality of life, increased long-term mortality, and an increased risk of chronic kidney disease requiring dialysis.[1-4] The mortality in cardiac surgery patients with AKI severe enough to require renal replacement therapy (RRT) can be as high as 60%.[5]

There are a number of causes and risk factors associated with AKI including poor preoperative cardiac function, diabetes, peripheral vascular disease, and female gender.[6] One of the putative agents associated with AKI in animal models receiving crystalloid fluids for resuscitative interventions is excess exogenous chloride ion (Cl⁻).[7, 8] As compared to non-Cl⁻ containing solutions in animal models, excess Cl⁻ appears to lead to a hyperchloremic metabolic acidosis, increased renal vascular resistance, reduced renal blood flow, and reduced glomerular filtration rate – all of which are injurious to kidney function.[9-11]

In non-cardiac surgery, including kidney transplantation, the use of low-chloride containing crystalloids leads to less acid-base and electrolyte perturbation.[12, 13] In trauma resuscitation, low Cl⁻ containing resuscitation solutions are also associated with more ideal acid-base status.[14]

Historically, one of the most common balanced salt-solutions used in adult cardiac surgery has been 0.9% normal saline (NS), a crystalloid solution with 154 mmol/L of Cl⁻. This is much higher than physiologic plasma levels of 103 mmol/L. Isolyte, a less commonly used crystalloid solution, is much closer to physiologic levels at 98 mmol/L Cl⁻. In the context of cardiac surgery, **there is no literature** expressly comparing the effects of balanced crystalloid solution such as Isolyte versus NS on AKI incidence. There is a single trial examining a low-Cl⁻ containing colloid solution in cardiac surgery that found less metabolic acidosis[15]; however, AKI or markers of AKI were not measured outcomes in that lone trial, so **it is not known whether low Cl⁻ solution will have any effect on AKI risk in humans.**

AKI results from a series of extremely complex cellular and molecular pathways involving endothelial, epithelial, inflammatory, and interstitial cells. The gold standard for identification and classification of AKI is dependent on serial serum creatinine (Scr) measurements[16], but this measurement can be unreliable during acute changes in kidney function.[17, 18] Recent studies have shown that tissue inhibitor of metalloproteinase (TIMP-2) performs better than existing markers for predicting the development of moderate or severe AKI (KDIGO stage 2 or 3) within 12 hours of sample collection.[19] To further enhance the sensitivity of utilizing TIMP-2, we plan on also measuring urinary insulin-like growth factor-binding protein 7 (IGFBP7). Along

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with TIMP-2, IGFBP7 is also an inducer of G1 cell cycle arrest, a key mechanism implicated in AKI.[19]

This study will utilize the urinary [TIMP-2]*[IGFBP7] multiplicative product as a composite biomarker index to investigate the impact of intraoperative infusion of NS versus Isolyte on post-cardiac surgery renal function. This biomarker should identify patients at risk of imminent (within 12 hours) AKI according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.[19, 20].

2.2. The investigators have not gathered preliminary data.

2.3. Patients presenting for cardiac surgery are already quite ill often with multiple comorbidities. Acute kidney injury in this population is associated with significant morbidity and mortality. The available literature indicates that a fairly simple intervention could *plausibly* reduce the incidence of AKI, but **it has not yet been examined in humans**. Generating an evidence basis for it will substantially improve the safety of patients who need cardiac surgery. This intervention to reduce AKI may also then be applied to the broader non-cardiac surgery population as well.

2.4. References:

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4. Mangano, C.M., et al., *Renal dysfunction after myocardial revascularization: risk factors, adverse outcomes, and hospital resource utilization. The Multicenter Study of Perioperative Ischemia Research Group*. Ann Intern Med, 1998. 128(3): p. 194-203.
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7. Zhou, F., et al., *Effects of fluid resuscitation with 0.9% saline versus a balanced electrolyte solution on acute kidney injury in a rat model of sepsis**. Crit Care Med, 2014. 42(4): p. e270-8.
8. Kellum, J.A., *Fluid resuscitation and hyperchloremic acidosis in experimental sepsis: improved short-term survival and acid-base balance with Hextend compared with saline*. Crit Care Med, 2002. 30(2): p. 300-5.
9. Modi, M.P., et al., *A comparative study of impact of infusion of Ringer's Lactate solution versus normal saline on acid-base balance and serum electrolytes during live related renal transplantation*. Saudi J Kidney Dis Transpl, 2012. 23(1): p. 135-7.
10. Wilcox, C.S., *Regulation of renal blood flow by plasma chloride*. J Clin Invest, 1983. 71(3): p. 726-35.

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13. Kim, S.Y., et al., *Comparison of the effects of normal saline versus Plasmalyte on acid-base balance during living donor kidney transplantation using the Stewart and base excess methods*. Transplant Proc, 2013. 45(6): p. 2191-6.
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15. Base, E.M., et al., *Efficacy and safety of hydroxyethyl starch 6% 130/0.4 in a balanced electrolyte solution (Volulyte) during cardiac surgery*. J Cardiothorac Vasc Anesth, 2011. 25(3): p. 407-14.
16. Bellomo, R., et al., *Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group*. Crit Care, 2004. 8(4): p. R204-12.
17. Jo, S.K., M.H. Rosner, and M.D. Okusa, *Pharmacologic treatment of acute kidney injury: why drugs haven't worked and what is on the horizon*. Clin J Am Soc Nephrol, 2007. 2(2): p. 356-65.
18. Mishra, J., et al., *Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery*. Lancet, 2005. 365(9466): p. 1231-8.
19. Meersch, M., et al., *Urinary TIMP-2 and IGFBP7 as early biomarkers of acute kidney injury and renal recovery following cardiac surgery*. PLoS One, 2014. 9(3): p. e93460.
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3. Study Design

- 3.1. This is a prospective, open-label, randomized, single center, controlled clinical study to determine the effect of intraoperative infusion of NS versus Isolyte on post-cardiac surgery on AKI event (renal injury) as measured by urinary [TIMP-2]*[IGFBP7] levels. After informed consent, we will randomly assign 30 trial-completing participants (potentially enrolling up to 40 to account for any dropouts) to the two study arms in a 1:1 ratio. We will compare the effect of electrolyte solution on patients' post- vs. preoperative [TIMP-2]*[IGFBP7] score differences with pairwise t-tests, and will similarly analyze routine demographic data and potential confounders, as well as secondary outcomes as listed below.
- 3.2. This is an open-label trial.

4. Inclusion and Exclusion Criteria

- 4.1. Participants will be drawn from the population of adult patients undergoing cardiac surgery at UNMH.

- 4.2. Inclusion criteria: consenting adult male and female patients undergoing non-emergent on- and off-pump cardiac surgery including: bypass grafting, valvular procedures, congenital defect correction, and thoracic aortic procedures or a combination of these procedures.

Exclusion criteria: emergency surgery, pregnancy, previous renal transplantation, documented moderate to severe AKI prior to enrollment (e.g. RIFLE-I or RIFLE-F/KDIGO stage 2 or 3), patients already receiving dialysis (acute or chronic) or in imminent need of dialysis at time of enrollment, subjects with chronic kidney disease without baseline serum creatinine value (baseline within 6 months of enrollment).

- 4.3. This study does not involve adults unable to consent, individuals who are not yet adults, pregnant women, or prisoners.
- 4.4. We will not exclude particular populations such as women, children, persons not fluent in English, any particular racial or ethnic groups, etc.

5. Number of Subjects

- 5.1. This is not a multicenter study; all recruitment will occur at UNMH.
- 5.2. We plan to recruit sufficient participants to obtain complete data on 30 subjects (15/group). We do not anticipate a high withdrawal rate, but may recruit as many as 40 to have a complete dataset of this size. Recruitment will stop upon attainment of the full sample of 30, or with the 40th consenting patient who at least begins study treatment (whichever comes first).
- 5.3. A power analysis with G*Power 3.1.9.2 software indicates that n=30 is sufficient in the context of a t-test to detect a difference between groups for the primary outcome that is roughly equal to the sample standard deviation. For (purely hypothetical) example, if the mean is 100 units and roughly 2/3 of the sample falls between 95 and 105, we would have 80% power to detect a treatment difference of 5 units.

6. Study Timelines

- 6.1. All data collection will occur in conjunction with clinically-indicated surgical care. The existence of this study will not affect the decision to refer for surgery, or the subsequent decision to proceed or not proceed with surgery, for any patient.
- Data collection will include pre-operative serum creatinine levels, which are very likely to already have been recorded for clinical reasons. The maximum pre-operative interval for this value will be six months (it is extremely unlikely that sufficiently recent serum creatinine data will be unavailable, but if this is the case, this value will be obtained prior to surgery). Other data will be gathered immediately prior to surgery, immediately after surgery, and up to 48 hours postoperatively. It is anticipated that all participants will already be in the hospital for all data collection.
 - A recruitment period duration of one year should be sufficient to recruit the targeted participant sample; we will apply for continuing review prior to study expiration if the target sample size is not met at that time.

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- Upon completion of data collection, the investigators anticipate one year for completion of all analyses, manuscript/presentation preparation, and submission of scholarly product to relevant outlets.

7. Study Endpoints

- 7.1. The primary outcome is the change in urinary [TIMP2]*[IGFBP7] composite from baseline to 24 hours postoperatively.

The secondary outcomes are:

- serum creatinine preoperatively and postoperatively at 24 and 48 hours,
 - serum chloride preoperatively and postoperatively at 24 and 48 hours,
 - clinically-determined need for dialysis prior to discharge, and
 - arterial pH, measured 24 hours after surgery.
- 7.2. This study involves assignment to receive one of two types of IV fluids, with data collection of laboratory values after surgery. When the laboratory values are available, it will no longer be possible to change the IV fluids received by the patient during surgery. Therefore, we have not identified any specific safety endpoints. All patients will receive routine clinical care intended to address all potential situations that arise during and as a result of surgery.
- 7.3. We have not identified any exploratory endpoints.

8. Research Setting

- 8.1. This research study will be conducted at the UNM Hospital and its surgical areas.
- 8.2. Potential subjects will be identified from among the investigators' routine patients who present for cardiac surgery.
- 8.3. Some data collection will involve the results of pre-existing laboratory orders; investigators will not necessarily have any influence over where participants have the pre-operative baseline serum creatinine labwork completed. Routine labwork will be completed in the main UNMH laboratory. The data for the TIMP2*IGFBP7 index will be obtained via assays conducted in co-investigator Dr. Vallabh Shah's laboratory at UNM HSC. The blood sample collection for these timepoints will occur in UNMH patient areas.
- 8.4. We do not plan to involve a community advisement board.
- 8.5. This research will not be conducted outside UNMH or its affiliates.

9. Resources Available

- 9.1. PI Dr. Neal Gerstein is an Associate Professor, and Medical Director of Cardiac Anesthesiology at UNMH. Dr. Lev Deriy is an Assistant Professor in the Anesthesiology department at UNM SOM. Dr. Vallabh Shah is an Associate Professor in both the departments of Internal Medicine and Biochemistry/Molecular Biology at UNM, and director of the Zuni Kidney Project. Dr. Nathan Lee is a CA-2 resident in Anesthesiology at UNM. Dr. Tim Petersen is the Research Information Specialist in the

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UNM Anesthesiology Department. All investigators have completed CITI and HIPAA certifications.

9.2. All clinical decisionmaking will be made by licensed providers at UNMH, in accordance with their areas of specialty and practice.

9.3. Other resources:

- UNMH performs many cardiac surgeries per month, and the recruitment period is likely to be completed in one year. The target sample size represents less than one consenting patient per week.
- All investigators have available time (non-clinical days, etc) for completion of research-related tasks as part of their routine job duties.
- UNMH already performs many cardiac surgeries per year, and is equipped with the personnel and other resources needed to provide appropriate care for these patients, including both routine care and care for any complications or other unexpected situations.
- All investigators will receive a copy of the HRRC-approved protocol and will participate in discussions about the research plan and logistics.

10. Prior Approvals

10.1. HRRC approval will be obtained before research activities commence.

10.2. The Departmental Review Form is included with this application.

10.3. This study does not involve ionizing radiation.

10.4. This study does not involve the collection of biological specimens for long-term storage. All blood and urine samples obtained will be destroyed as appropriate upon completion of individual lab analyses.

10.5. This study will be listed on ClinicalTrials.gov.

11. Multi-Site Research

11.1. This is not multi-site research.

12. Study Procedures

12.1. Consenting patients will be randomly assigned to receive either Isolyte-S balanced crystalloid or normal saline for intraoperative maintenance and resuscitation fluids. The amount administered is left to the discretion of the clinical providers, according to usual clinical criteria and practice. Other than the product selection of normal saline vs. Isolyte, this study presents no changes to patient treatment.

- Consenting patients will be randomly assigned to receive either Isolyte-S or normal saline solution in the perioperative period, in an amount determined by the provider for clinical reasons. Data to be gathered include basic demographic data, surgery type, and certain laboratory values. Lab data to be gathered include serum creatinine levels preoperatively, as well as levels of TIMP2, IGFBP7, serum creatinine, serum chloride, and arterial pH at timepoints as defined in the primary and secondary outcome measures listed above. The need for dialysis (clinically determined by an attending physician independently of this research study) prior to discharge will also

- be recorded. The outcome measures are intended to indicate risk for or actual acute kidney injury.
- Both normal saline and Isolyte-S (B Braun Medical Inc., Bethlehem PA, USA)) are legally marketed in the United States, and FDA approved for this indication (fluid maintenance). Providers already have clinical discretion to administer either normal saline or Isolyte-S in the setting of cardiac surgery, and it is normal practice to administer electrolyte-containing fluids intravenously during these surgeries.
 - Subjects will not be asked to complete a questionnaire or otherwise volunteer information.
 - All study data will be sourced from patient medical records, except for the TIMP2 and IGFBP7 laboratory values.
 - The preoperative serum creatinine test is part of routine practice, and is expected for all preoperative cardiac surgery patients. Intraoperative fluid maintenance is routine for surgical patients, and providers already have clinical discretion to administer normal saline or Isolyte-S. Arterial blood pH monitoring is also routine for these patients. The remaining data consists of laboratory values. Routine labwork (including all of the lab-based secondary outcome measures) is an expected part of cardiac surgery patients' postoperative care. The TIMP2*IGFBP7 index will be obtained in addition to routine postoperative monitoring; routine postoperative labwork (e.g. to assess kidney function) is not being replaced.
 - This is not a humanitarian-use device study.
 - There will be an interim review of all study data after completion of the 20th participant, in an effort to detect any unusual patterns of morbidity/mortality. All outcomes will be analyzed. The study will be suspended if this interim review detects a statistically-significant difference is detected between study arms with respect to the clinically-determined need for dialysis prior to discharge.

13.Data Analysis

- 13.1. The primary outcome involves a composite index: the product of urinary TIMP2 and IGFBP7 values. For a given patient, this index will be calculated for preoperative values and for postoperative values as described above, and the difference between pre- and postoperative index values will be recorded as the primary outcome. A t-test (or Wilcoxon-Mann-Whitney test, in the case of nonnormal distributions) will be used to evaluate the hypothesis. Secondary outcomes that similarly involve pre- vs. postoperative changes in laboratory values (serum creatinine and serum chloride) will be tested in the same fashion. The 24-hour arterial pH data will be assessed with t-test or Wilcoxon-Mann-Whitney as appropriate depending on distribution normality. The clinically-determined need for dialysis prior to discharge will be assessed with Fisher's Exact test.
- 13.2. A power analysis with G*Power 3.1.9.2 software indicates that this sample size is sufficient in the context of a t-test to detect a difference between groups for the primary outcome that is roughly equal to the sample standard deviation. For (purely hypothetical) example, if the mean is 100 units and roughly 2/3 of the sample falls between 95 and 105, we would have 80% power to detect a treatment difference of 5 units.

14. Provisions to Monitor the Data to Ensure the Safety of Subjects

- 14.1. Both normal saline and Isolyte have been used routinely in cardiac procedures for many years, nationally and at UNMHSC, and both have excellent safety records. The PI Dr. Neal Gerstein and co-investigators will conduct an interim review of patient records upon completion of data collection for the 20th participant, in an effort to detect substantial differences in outcomes.
- 14.2. All study data will be reviewed.
- 14.3. Both normal saline and Isolyte have been safely used in cardiac surgery for many years. It is exceedingly unlikely that scientific literature would indicate a substantial difference in risk posed by these two solutions; however, as Chief of Cardiac Anesthesia at UNMH, Dr. Gerstein routinely reviews scientific/medical literature related to cardiac surgery.
- 14.4. Patient records will be reviewed for unusual patterns of morbidity/mortality. In addition, all outcomes will be analyzed with the above-described statistical tests.
- 14.5. The study will be suspended if a statistically-significant difference is detected in the interim analysis between study arms with respect to the clinically-determined need for dialysis prior to discharge.
- 14.6. The HRRC will be notified if the suspension criterion is met.

15. Withdrawal of Subjects

- 15.1. We have not identified any likely circumstances in which subjects may be withdrawn from the study without their consent. However, there is a very unlikely chance (<1%) of an unforeseen situation in the process of administering the fluids that may bias the results; data for any affected patients would be omitted from the final analysis.
- 15.2. Consenting participants may withdraw at any time. If medically appropriate in the clinical judgment of the attending physicians, the IV fluid solution may be changed upon participant-initiated withdrawal. This change would not require any tapering of dosage or laboratory tests. Data collection would simply cease.
- 15.3. We do not anticipate any partial withdrawals from arm assignment only, but participants who wish to withdraw from arm assignment and for whom the IV fluid is changed per the providers' clinical judgment will also be removed from data collection efforts in order to maintain data consistency. If an enrolled patient elects this type of partial withdrawal after IV fluid administration begins and the fluid is not changed per the providers' clinical judgment, data collection will continue as usual because there is no effective change to treatment. After arm assignment, details of the administration of IV fluids (e.g. flow rate, duration, etc) are always left to the discretion of the attending physicians, so post-withdrawal IV fluid administration will not change in a specified way.
- 15.4. Data for participants who elect to withdraw completely will be omitted from analysis. Any already-gathered data will be maintained for purposes of safety review and oversight, but identifiers will be removed upon withdrawal. Specimens will be appropriately discarded upon patient withdrawal regardless of data collection status.

15.5. Participants who elect to withdraw simply need to say so to an investigator.

16.Data Management/Confidentiality

- 16.1. The research team will use their HSC-granted access to PowerChart to access patient medical records to obtain the data listed in this protocol, and also obtain data from laboratory values.
- 16.2. Direct identifiers will be used temporarily in order to link the study-specific laboratory data to the data obtained from the medical record, and in order to permit accurate data collection from only consenting patients' medical records.
- 16.3. The research requires the use of Protected Health Information, but not its disclosure to individuals who are not on the approved study team (except as may be required by law).
- 16.4. The data do not include information that is typically considered to be sensitive.
- 16.5. A Certificate of Confidentiality will not be pursued for this study.
- 16.6. All investigators are HIPAA-trained, and all identifiable electronic data will remain on UNM HSC password-protected servers. All data will be deidentified upon completion of data collection. Paper data collection forms bearing identifiers will be maintained in a locked cabinet in Anesthesiology department offices. Upon completion of data collection, deidentified data will be entered to a spreadsheet maintained on UNM HSC password-protected servers. When this step is complete, all data forms bearing identifiers will be securely shredded, leaving only deidentified data for analysis.
- 16.7. Data will not be coded.
- 16.8. Datasheets will be maintained until the completion of data collection. Data may be spot-checked at this point against the medical record, and any incomplete or illegible entries will be rectified by reference to the medical record.
- 16.9. Identifiable data will not be transferred or transmitted to outside entities.
- 16.10. Identifiable data will not be collected, transmitted, or stored via the internet.
- 16.11. Data will not be collected by audio or video recording.
- 16.12. Data will not include photographs.

17.Data and Specimen Banking

- 17.1. Upon completion of data collection, all study data will be deidentified. Deidentified data may be maintained indefinitely for future use, e.g. to provide underlying data for a future power analysis.
- 17.2. This is not a multicenter study; all data will be maintained locally on password-protected UNM HSC servers.

18.Risks to Subjects

- 18.1. The primary risk to participants is posed by randomization. The current evidence is hypothetical and thus not sufficient to make a clear determination as to the relative

safety of normal saline vs. Isolyte for cardiac surgery patients, or the extent to which they may or may not reduce kidney-related complications of surgery.

18.2. Both normal saline and Isolyte are in widespread use for fluid replenishment during surgery, with excellent safety records.

18.3. Risks to embryos and fetuses are not relevant here; pregnancy is an exclusion criterion.

18.4. There are no appreciable risks to others who are not subjects.

18.5. Steps taken to minimize the probability or magnitude of risks include: selection of FDA-approved IV fluids for the study, the open-label nature of the study, permitting provider discretion in amounts administered, gathering as much study data as possible from the already-existing medical record, maintaining routine labwork to forewarn providers of developing kidney problems, and exclusion of patients known to have kidney problems.

19. Potential Benefits to Subjects

19.1. We have not identified any benefits that will accrue to all subjects. If one of the two IV fluids is superior to the other, patients randomized to receive it may experience benefit. The existence and nature of these benefits is not currently known, but because both normal saline and Isolyte are currently in widespread use for intraoperative fluid maintenance without known major problems, any benefit is expected to be small and only detectable at the group level.

20. Recruitment Methods

20.1. Potential subjects who are already inpatients will be recruited in patient rooms at UNMH the night before surgery. For patients who arrive at the hospital on the day of surgery, recruitment will occur in the pre-operative holding areas.

20.2. Investigators will identify potential subjects from their regularly-scheduled case load, and apply the inclusion/exclusion criteria to the extent possible prior to making research-related contact with a patient.

20.3. No recruitment materials are planned. Potential participants will be provided a copy of the consent form for their review and consideration during the recruitment process. Consenting participants will be provided a copy of the completed form.

21. Provisions to Protect the Privacy Interests of Subjects

21.1. Cardiac surgery patients who meet the inclusion/exclusion criteria will be asked to consider participation in a research study while in the pre-operative holding area. This area is already used for private doctor/patient conversations, so it provides sufficient privacy for research conversations. This conversation will consist only of study introduction and the consent process, because patients do not need to personally provide any information for this study. Similarly, this study does not involve patients being observed or otherwise experiencing anything beyond their expected surgery. All data to be gathered will be obtained from the patients' medical records, in a secure HSC area by personnel authorized by virtue of their job responsibilities to access these records.

22. Economic Burden to Subjects

Research Procedures	Number of Samples/Procedures	Responsible Party	
		Study	3 rd Party Payer or Participant
Normal saline or Isolyte for IV fluids	<u>All</u>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Laboratory analysis of TIMP2 and IGFBP7	<u>All</u>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
		<input type="checkbox"/>	<input type="checkbox"/>
Standard of Care Procedures	Number of Samples/Procedures	Responsible Party	
		Study	3 rd Party Payer or Participant
<u>All other elements of surgery, hospitalization, and associated care</u>	<u>All</u>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
<u>All labwork other than TIMP2 and IGFBP7</u>	<u>All</u>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
		<input type="checkbox"/>	<input type="checkbox"/>

22.1. All research activities for this study, save the TIMP2 and IGFBP7 assays, occur in the context of routine care for cardiac surgery patients. All relevant costs are listed above.

22.2. Both normal saline and Isolyte are already approved for use in this context, and depending on providers' clinical preference, either of them may be used for any cardiac surgery patient at UNMH. Relevant patients are already expected to receive one or both of these types of IV fluids, regardless of participation in this study. The difference in participant costs is relatively small: most patients are expected to receive 4 or fewer 1L bags of fluids. Normal saline costs approximately \$2.50, and Isolyte costs approximately \$25.

22.3. Patients will be responsible for paying for treatment of adverse events.

22.4. Relevant costs are described in the consent form.

23. Compensation

23.1. Participants will not be compensated for their participation.

24. Compensation for Research-Related Injury

24.1. Research-related injury is not anticipated, and we do not have dedicated funds available to compensate in the unlikely event of research-related injury. This information is contained in the consent form.

25. Consent Process

25.1. Consent will be obtained for participation in this study.

25.1.1. Only qualified study team members will obtain consent. All study team members are qualified to discuss medical information with patients and have HIPAA certification.

25.1.2. The consent process will occur in patient rooms or the preoperative holding areas. To provide for privacy, the consent conversation will begin with a simple question about whether the patient has interest in participating in a research study.

- 25.1.3. Coercion and undue influence will be minimized by the absence of participant compensation, and by reassurances from the study team that patient care will be unaffected by the patient's participation choice.
- 25.1.4. Inpatients will be able to consider participation overnight. Patients who arrive at the hospital on the day of surgery will be able to consider participation for most of the duration of their stay in the preoperative holding area (after study introduction). As any difference in risk and benefit is expected to be very small, this period of time should suffice for most patients. Any patients who cannot come to a decision in this time will be excused from participation, and receive IV fluids according to the provider's clinical judgment.
- 25.1.5. The study intervention occurs over the duration of surgery. Ongoing consent should not be an issue, but any expressed desire to withdraw will be acted upon as soon as is practical.
- 25.1.6. The study team member obtaining consent will describe the study and consent material carefully, but as this study involves a relatively simple intervention, will not take specific steps to enhance understanding.
- 25.1.7. The study team member obtaining consent will ask the potential participant to describe the planned intervention, randomization, and risks/benefits to ensure understanding.

Subjects not fluent in English

- 25.1.8. We do not anticipate enrollment of large numbers of patients who do not speak English. We expect that Spanish would be the most common alternative language spoken by potential participants.
- 25.1.9. If any enrolled participants have limited fluency in English, consent will be obtained with the HRRC's standard short-form consent document for these enrollments. Translation into a language suitable for the participant will occur via the same channels as routine clinical conversations: e.g. the official UNMH translation service, a bilingual family member whose presence is approved by the prospective participant, and/or bilingual UNMH staff.

Cognitively Impaired Adults/Adults Unable to Consent/Use of a Legally Authorized Representative

- 25.1.10. We do not plan to enroll participants who are cognitively impaired, unable to consent, or who require the use of a legally authorized representative.

Subjects who are not yet adults (infants, children, teenagers)

- 25.1.11. Only adults will be enrolled.

Waiver or Alteration of Consent Process (consent will not be obtained, required element of consent will not be included, or one or more required elements of consent will be altered)

- We are not requesting waiver or alteration of the consent process.

26.Documentation of Consent

- 26.1. Consent will be documented; the form is included with this application.
- 26.2. This study does not involve the storage of tissue samples.

27.Study Test Results/Incidental Findings

- 27.1. **Individual Results:** Nearly all of the clinical data to be obtained for this study are already gathered as part of routine medical care. Any important individual results indicated by these data will already be communicated with patients, consistent with routine medical care. The TIMP2 * IGFBP7 index used here is likely to be an indicator of outcomes relevant to the care of post cardiac surgery patients, but it has not yet been validated so it is of little utility outside the research context. Individual results of note for all lab results are typically communicated to patients, but usually implicitly (e.g. reference to overall “labwork”), in connection with routine care. The specific index result may or may not be calculated prior to patient discharge.
- 27.2. **Incidental Findings:** All data to be recorded for this study are relevant to patients’ postoperative care, and most are already gathered as part of routine medical care. Only the TIMP2 * IGFBP7 index is specific to this research (this test is only available in the context of research). Any results that fall outside expected ranges would inform ongoing medical treatment. This study does not involve imaging, genetic sequencing, or other technique likely to generate incidental findings. We do not anticipate any incidental findings being produced by this study.

28.Sharing Study Progress or Results with Subjects

- 28.1. This study does not involve ongoing treatment, so there would be little benefit to informing participants of overall study results while the study is underway. Similarly, even if any preliminary results were available, the resultingly small sample size would reduce their reliability. Accordingly, we do not plan to share preliminary study results with subjects.
- 28.2. We do not plan to provide subjects with a summary of study results after the study is complete, because study data will be deidentified upon completion of data collection, and it will not be possible to identify participants when the final results are available. It would also not be possible to change the IV fluids that the patient had received during surgery. Similarly, this study does not involve collection of long-term outcome data, so it will not be possible to provide patients with information about any future risk.

29.Inclusion of Vulnerable Populations

- 29.1. This research does not involve vulnerable populations.

30.Community-Based Participatory Research

- 30.1. This study does not involve community-based participatory research.

31.Research Involving American Indian/Native Populations

- 31.1. This study does not target American Indian/Native populations.

32.Transnational Research

32.1. This study does not involve transnational research.

33. Drugs or Devices

33.1. Both normal saline and Isolyte-S are routinely handled by the UNMH Pharmacy and licensed UNMH providers. Since this is an open-label study, we will not modify standard procedures surrounding drug storage, handling, or administration. All study medications will be administered by authorized UNMH personnel following routine procedures.

33.2. This study does not involve an investigational drug because both normal saline and Isolyte are already approved for intravenous fluid maintenance; there is no IND for this study.

33.3. The Drug Attachment is included with this application.

33.4. This is not a device study.

Checklist Section

This section contains checklists to provide information on a variety of topics that require special determinations by the IRB. Please complete all checklists relevant to your research.

I. Waivers or Alterations of Consent, Assent, and HIPAA Authorization

We are not seeking a waiver or alteration of consent or HIPAA authorization.

II. Vulnerable Populations

This research does not involve vulnerable populations.

III. Medical Devices

This study does not involve medical devices.