OPTIMAL PROTAMINE DOSING FOR HEPARIN REVERSAL FOLLOWING CARDIOPULMONARY BYPASS: A BLINDED RANDOMIZED CONTROL TRIAL COMPARING TWO STRATEGIES

IRB: 20220234

PROTOCOL VERSION 1

MAY 5, 2022

PRINCIPAL INVESTIGATOR: DR. MICHAEL FABBRO

NCT: NCT05426031

Objectives:

The primary objective is to compare two protamine dosing strategies in cardiac surgical patients. A fixed dosing strategy, using 250 mg of intravenous (IV) protamine, will be compared to a standard dosing strategy of 1mg IV protamine for every 100 IU of heparin given before the initiation of cardiopulmonary bypass (CPB). Only patients with calculated protamine doses over 250 mg will be included. The primary outcome is mean difference in activated clotting time between baseline and reversal of heparin. Secondary outcomes will include additional protamine dosing, chest tube output and units of packed red blood cells transfused.

Additionally, a retrospective review of protamine and heparin dosing will be performed using existing data. This will be done to compare prospective randomized results to our historical practices.

Background:

Currently, protamine dosing for heparin reversal following cardiopulmonary bypass varies highly among centers, and even among practitioners in a given center. Reversal practices include heparin ratio-based dosing, heparin concentration based dosing, and formulaic dosing based on calculations utilizing values like activated clotting time (ACT).[1] These variations in practice seek to address two primary concerns. The first concern is inadequate reversal of heparin following cardiac surgery, leading to bleeding in a patient group at high risk for bleeding and transfusion.[2] The second concern these variations seek to address is overdosing of protamine, which has also been shown to increase measures of clinical bleeding.[3] In the COVID era a third concern has arisen which is drug shortages.

Each of these strategies has advantages and disadvantages. Protamine dosing based on heparin ratios are simple and the most widely employed. There is variation even within this practice since ratios can be based on initial heparin dose or total dose, and heparin dosing itself can be based on ideal or total body weight. The most common form of ratio-based dosing is 1mg protamine to every 100 IU of heparin given before initiation of cardiopulmonary bypass (CPB). Evidence suggests that lower ratios may be just as effective at reversal with no increase in bleeding measures.[4] While heparin concentration-based dosing objectively determines protamine doses, point-of-care devices for this purpose remain expensive and unavailable in many institutions including ours. Furthermore, the benefit of this strategy remains controversial.[1] Some guidelines support this method with low quality evidence behind the recommendation.

Current guideline recommendations for heparin dosing incorporate low quality evidence to support weight-based dosing.[5] A commonly cited dose is 300 units/kg of actual body weight. A previous analysis of heparin and protamine dosing strategies have identified an average patient weight of 78 kg, and 91-105 units of heparin per 1 mg of protamine (heparin: protamine ratio), depending on the protamine dosing strategy.[6] With 300 units/kg and average body weight these ratios would result in an 230-260 mg of protamine doses. Current practices which often employ higher heparin dosing strategies, up to 400 units/kg actual body weight, and 1 mg protamine per 100 units of heparin, often result in much higher protamine doses than this. Some studies supporting low

---

[1] Hecht, P., Besser, M., & Falter, F. (2020). Are We Able to Dose Protamine Accurately Yet? A Review of the Protamine Conundrum. *The journal of extra-corporeal technology*, *52*(1), 63.

[2] Hajjar L a, Vincent J-L, Galas FRBG, et al. Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. *JAMA*. 2010;304(14):1559-1567. doi:10.1001/jama.2010.1446.

[3] Boer, C., Meesters, M. I., Veerhoek, D., & Vonk, A. B. A. (2018). Anticoagulant and side-effects of protamine in cardiac surgery: a narrative review. *British journal of anaesthesia*, *120*(5), 914-927.

[4] Meesters, M. I., Veerhoek, D., de Lange, F., de Vries, J. W., de Jong, J. R., Romijn, J. W., ... & Boer, C. (2016). Effect of high or low protamine dosing on postoperative bleeding following heparin anticoagulation in cardiac surgery. *Thrombosis and haemostasis*, *116*(08), 251-261.

[5] Shore-Lesserson, L., Baker, R. A., Ferraris, V., Greilich, P. E., Fitzgerald, D., Roman, P., & Hammon, J. (2018). STS/SCA/AmSECT clinical practice guidelines: Anticoagulation during cardiopulmonary bypass. *The journal of extra-corporeal technology*, *50*(1), 5.

[6] Shore-Lesserson, L., Reich, D. L., & DePerio, M. (1998). Heparin and protamine titration do not improve haemostasis in cardiac surgical patients. *Canadian journal of anaesthesia*, *45*(1), 10-18.

protamine ratios, 0.8 mg per 100 units of heparin, have average protamine doses as high as 329 mg, again demonstrating variation in heparin practices.[7]

In addition to variation, another concerning feature of protamine ratio dosing based on initial heparin dose is heparin pharmacology. The effective half life of heparin is 60-90 minutes.[8] This can be further increased for larger heparin doses used in the context of CPB. In a study of over 4000 patients, average CPB times exceeded 100 minutes.[9] With this considered, the pharmacokinetics of heparin do not support the use of initial heparin doses to calculate protamine dosing. Indeed, in a recent randomized controlled trial, patients randomized to receive post CPB protamine doses based on a mathematical model of heparin clearance were administered significantly lower doses of protamine without any difference in viscoelastic testing or bleeding end points.[10] Lastly, protamine is available in two vial configurations, 250 mg and 50 mg. In times of critical medication shortages, as seen in pandemics, doses exceeding 250 mg require the use of additional protamine vials.

The intent of this investigation is to address the following concerns: the expense of heparin concentration monitoring and controversial evidence supporting its use, variation in practice with ratio dosing strategies, lack of pharmacological support for use of heparin initiation doses for protamine dosing, and lastly, medication shortages. Our hypothesis is that standard heparin dosing, 350 units/kg actual body weight with fixed protamine dosing, 250 mg, will be non-inferior to a conventional ratio-based protamine dosing strategy of 1 mg protamine per 100 units of heparin in patients with calculated protamine doses over 250 mg. We also hypothesize that the fixed dosing group will receive less protamine overall. The outcomes of interest are primarily the pre CPB to post CPB ACT ratio, and secondarily, additional protamine administration and chest tube output.

Inclusion Criteria:

- Patients greater than or equal to 18 years of age undergoing elective cardiac surgery with cardiopulmonary bypass.
- Patients must have a calculated protamine dose greater than 250 mg based on standard 1:1 initial heparin to protamine dosing calculation.

Exclusion Criteria:

- Patients who are under 18 years of age or pregnant.
- Patients undergoing emergency surgery (ASA class E)
- Patients with known coagulation disorders.
- Patients requiring circulatory arrest or deep hypothermia.
- Patients who have not had the appropriate interruption in coumadin, direct oral anticoagulants or non-aspirin antiplatelet agents.
- Patients on pre-operative intravenous unfractionated heparin infusions.
- Patients ineligible for heparin administration due to known adverse reactions including allergy or heparin induced thrombocytopenia or known heparin resistance.
- Patients who are unable to provide informed consent in the form of a signature.
- History of adverse reaction to protamine.
- Have any condition that, in the opinion of the investigator, will compromise the well-being of the patient or the study, or prevent the patient from meeting or performing study requirements.

---

[7] Meesters, M. I., Veerhoek, D., de Lange, F., de Vries, J. W., de Jong, J. R., Romijn, J. W., ... & Boer, C. (2016). Effect of high or low protamine dosing on postoperative bleeding following heparin anticoagulation in cardiac surgery. *Thrombosis and haemostasis*, *116*(08), 251-261.

[8] Tahir R. A review of unfractionated heparin and its monitoring. US pharm. 2007;32(7):26-36.

[9] ElBardissi, A. W., Duclos, A., Rawn, J. D., Orgill, D. P., & Carty, M. J. (2013). Cumulative team experience matters more than individual surgeon experience in cardiac surgery. *The Journal of thoracic and cardiovascular surgery*, *145*(2), 328-333.

[10] Miles LF, Burt C, Arrowsmith J, McKie MA, Villar SS, Govender P, Shaylor R, Tan Z, De Silva R, Falter F. Optimal protamine dosing after cardiopulmonary bypass: The PRODOSE adaptive randomised controlled trial. PLoS medicine. 2021 Jun 7;18(6):e1003658.

Procedures involved:

Following written informed consent, a predicted protamine dose will be calculated based on a 1mg of protamine to each 100 units of heparin (heparin dosing will follow 350 u/kg). Any patient with a calculated dose over 250mg will be randomized to one of two groups; standard protamine dosing of 1mg per 100 units of pre-CPB heparin dose or fixed dosing of 250 mg. The cardiac surgery procedure will commence, with 350 units/kg of heparin used for initiation of cardiopulmonary bypass. This is based on our centers anecdotal experience of 300 units/kg being inadequate. Additional heparin (in aliquots of 50 units/kg) will be administered prior to CPB initiation if the target Activated Clotting Time (ACT) of 450 seconds is not achieved. Pharmacy will prepare blinded protamine dose based on the group each patient is assigned to. Following discontinuation of bypass protamine will be administered centrally and slowly based on standard clinical practice. ACT will be measured after protamine administration in standard fashion. Additional protamine administration will be at the surgeon and anesthesiologists' discretion based on post bypass ACT and bleeding. Transfusion practices will follow current protocol.

Data Banking:

The study team intends to store only data from this study, for future research and retrospective analysis of it.

All data for each patient will be recorded on an individual study sheet by the assigned anesthesia personnel caring for the patient. Once each enrollment is completed data sheets will be collected by study investigators and placed in in individual study folders and locked in a Department of Anesthesia faculty office. Data will subsequently be transferred and stored on a University of Miami network computer in compliance with the Electronic Data Quality Policy for Clinical Research.

Data Stored:

- Patient age
- Surgery type
- ASA status
- Preoperative INR
- Pre-cardiopulmonary bypass ACT
- Post-cardiopulmonary bypass ACT
- Patient's weight
- Initial heparin dose
- Total heparin dose
- Initial protamine dose
- Additional protamine dose
- Total Protamine dose
- Time each sample is collected and reported will be recorded
- Packed blood cells units transfused intraoperatively
- Fresh frozen plasma units transfused intraoperatively
- Platelets units transfused intraoperatively
- Cryoprecipitate units transfused intraoperatively
- 4 hour and 24-hour chest tube output

Data collection and release:

Anesthesiologists will administer heparin and protamine in standard fashion. Activated clotting times will be measured by perfusionists in standard fashion. Protamine dose preparation will occur in the UHealth Tower pharmacy for the purposes of blinding and standardization.

Data access will be limited to the listed study investigators only. All investigators will complete required CITI training. Data will be stored on study sheets in individual patient folders locked in anesthesia office with access available to principal investigator only. Original consent forms will be kept in subject study charts, with a copy given to all subjects and a second copy placed in the medical charts. All study charts, regulatory binders will be stored at the Research office located at University of Miami Hospital, 1400 NW 12th Avenue, Room 3075J. Miami, FL 33136.The data will be transferred to a password protected University of Miami computer in the department of anesthesia. The excel sheet data will be made available to investigators through password protected excel document.

All study records and documents, will be retained for studies that are subject to both FDA and HIPAA regulations: According to HIPAA regulations will be retained for a minimum of six (6) years following study closure. Our research department will retain all research data until the later of any of these possible dates listed above.

Data Management:

Total number of subjects: 130

Using retrospective sample data and STATA v 17.0 and considering a power = 0.80 and alpha = 0.05 and equal randomization to control and experimental groups, and 1 pre and 1 post intervention (protamine) measurement the sample sizes required to be able to detect a 2-sided difference between groups of 5, 10, or 15 were as follows[11]:

DD power calc: n= 230 mde= 5 power=.8 p=.5 pre=1 post=1 depvar=act
DD power calc: n= 59 mde=10 power=.8 p=.5 pre=1 post=1 depvar=act
DD power calc: n= 27 mde=15 power=.8 p=.5 pre=1 post=1 depvar=act

Previous studies comparing ACT devices have used a difference of 10 seconds as clinically meaningful.[12] To detect a difference of 10, we would need to be powered to 118 subjects. We have chosen 130 subjects to account for any patients with incomplete data or that need excluded after enrolment for any reason.

Risks to subjects:

This study poses minimal risk to patients. Additional heparin will be administered to ensure an ACT > 450 seconds prior to initiation of CPB. Additional protamine will be administered after the initial post CPB dose if the ACT values are greater than 20% of baseline, or if there is concern for clinical bleeding.

Potential Benefits

Direct potential benefits cannot be guaranteed to the patients. This is a study that seeks to compare a type of protamine dosing strategy and increase the knowledge of heparin reversal in cardiac bypass surgery.

---

[11] Burlig F, Preonas L, Woerman M. Panel data and experimental design. Journal of Development Economics. 2020 May 1;144:102458.

[12] Li H, Serrick C, Rao V, Yip PM. A comparative analysis of four activated clotting time measurement devices in cardiac surgery with cardiopulmonary bypass. Perfusion. 2021 Sep;36(6):610-9.

Vulnerable Populations:

This study will not include any vulnerable patient population. Pregnant women, prisoners and patients unable to provide consent in the form of a signature will be excluded

Setting:

Research consents will be obtained in the operating room holding area of University of Miami Hospital for patients admitted the day of surgery. In hospital patients will be consented the night prior to surgery in their admitted locations. Heparin and protamine administration, and ACT measurements will take place within the Operating Room, as is standard. Post-surgical care and monitoring including blood product administration and chest tube output recording will be conducted in the intensive care unit

Resources available:

Dr. Michael Fabbro Assistant Professor of Anesthesiology. He is a board certified cardiac anesthesiologist who has conducted previous research as the principal investigator in the area of coagulation. Namely he has previously written IRB's and provided oversight for research comparing viscoelastic testing measures to routine laboratory tests similar to the proposed study design. Dr. Fabbro will be responsible for the recruitment and consent of all test subjects. He will oversee the collection and testing of all samples. Lastly he will be collecting, storing and dissimilating data to other investigators. He will be responsible for constructing the manuscript.

Dr. Pankaj Jain is an Associate Professor of Anesthesiology and is a board certified cardiac anesthesiologist. Dr. Jain has participated in and published on coagulation issues in cardiac surgery patients. He will be assisting in the recruitment and consent of all test subjects. He will also assist in the collection and testing of all samples. and provide substantial contribution to the manuscript.

Dr. Richard Epstein is Professor of Anesthesiology and a board certified anesthesiologist. Dr. Epstein has prolific publications on statistical methods and analyses and will be providing the statistical analysis.

Kabir Bedi is a medical student at the University of Miami. He will be assisting in consenting, data collection and manuscript editing.

Dr. Alejandra Silva is an International Medical Graduate currently working as Research Coordinator for the Anesthesia Department. She will be assisting with IRB submission, consenting, data collection, and manuscript editing.

Patient Recruitment Methods:

Potential subjects will be identified using the daily released operating room schedule. Patients on the schedule will be pre-screened using available medical data for exclusion criteria. If patients do not meet any of the exclusion criteria they will be visited by the Principal Investigator, Sub-investigator and/or Study coordinators on the morning of surgery or the night before depending on their admission status. If the subject is currently an inpatient at the hospital, the medical team taking care of the patient will be approached by the study team to get permission to approach the subject. Study details, risks, benefits and alternatives will be discussed with each potential subject. If the patient shows interest into the study, the PI will notify research personnel of potential participant to start the process of consent. Study information and informed consent document (attached) will be provided to each subject. If the patient agrees to the study a copy of the signed consent will be provided to the patient and one placed in the patient medical chart. The original document will be placed in the study specific subject folder.

Study End Point:

Primary Outcome: Mean difference in activated clotting time
Primary Outcome Measure Description: Activated clotting time is going to be measured with the Hemocron Elite device (point of care).
Primary Outcome Measure Timeframe: two time points: once before incision and five minutes after protamine administration.

Secondary outcome: additional protamine dosing
Secondary outcome Measure Description: measured in mg.
Secondary outcome Measure Timeframe: the additional amount of protamine used on the patient will be added and recorded at the end of surgery.

Secondary outcome: chest tube output
Secondary outcome Measure Description: measured in mL
Secondary outcome Measure Timeframe: measured since the beginning of surgery for 24 hours

Secondary outcome: units of red blood cells transfused
Secondary outcome Measure Description: measured in units
Secondary outcome Measure Timeframe: measured only during the time of surgery.

Confidentiality:

Data will be recorded on study sheets locked in the Department of Anesthesia in a locked filing cabinet for the period of one year. Additionally, data will be stored on a password protected University of Miami computer in the Department of Anesthesia. Data will remain in a password protected excel sheet with access provided only to investigators listed on the IRB protocol. All study records and documents, will be retained for studies that are subject to both FDA and HIPAA regulations: According to HIPAA regulations will be retained for a minimum of six (6) years following study closure. Our research department will retain all research data until the later of any of these possible dates listed above.

(a). ☒ Data will be collected from the EMR or subjects at UHealth or JHS.

☒ Research Subjects will sign a HIPAA Authorization before the research will collect this data.

☐ Research Subjects will not sign a HIPAA Authorization for this data collection and the research is requesting a waiver of HIPAA authorization from the IRB. (Complete Section 17 below)

(b). Data collected:

☒ Will not include Protected Health information or Personally Identifiable Information

☐ Will include Protected Health information or Personally Identifiable Information

(c). How will the research store the data?

☒ On a University of Miami electronic device (e.g. encrypted, password-protected computer)

☐ On a cloud-based storage system that is approved by the University of Miami

☒ Other, specify: Data will be recorded on study sheets locked in the Department of Anesthesia in a locked filing cabinet for the period of one year.

Select one of the following:

☐ The Principal Investigator (and/or Study Team members) will record (e.g. write down, abstract) data acquired in a manner that **does not include any** indirect or direct identifiers (listed in the instructions for Section 15 of this protocol), and the recorded data will not be linked to the individual's' identity.

OR

☒ The Principal investigator (and/or Study Team members) will record (e.g. write down, abstract) the data collected in a manner that does not include any direct identifiers (see list in the instructions for Section 15 of this protocol) of any subject. Instead, the Principal Investigator and/or Study Team members shall will assign a code (that is not derived in whole or in part from any direct or indirect identifiers of the individual) to each study subject and link the code to the study subject's identity. **The link to each subject's identity and/ or other identifiable information will be maintained on a document separate from the research data.**

Biospecimens

☒ Not applicable. No biospecimens will be collected

☐ *Bio*-Specimens obtained for this research will be stored without any direct or indirect identifiers.

☐ *Bio*-Specimens obtained for this research will be stored in a de-identified coded manner.

☐ When required to transport data or bio-specimens for this research, the research team will transport the data and bio-specimens in a de-identified (or anonymous) manner with a link to the individual subject's identity maintain separately from the data and/or bio-specimen.

Authorization for Use and Disclosure of Protected Health Information (HIPAA)

Type of Request:

☒ Waiver of Authorization for access to medical record for subject identification/recruitment.

☐ Waiver of Authorization for access to medical record to obtain data for the research.

Confirm that you will destroy or de-identify the information you collect at the earliest opportunity.

☒ ***I confirm***

Confirm that the information you collect will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study or for other research for which the use or disclosure of PHI is permissible.

☒ ***I confirm***

Provision to Protect Privacy Interests of Subjects:

Study information packets and consent forms (attached) provided to each patient will list all investigators and will provide immediate contact information for the principal investigator. Subjects will be advised that the can withdrawal from the study at any time point. If subjects withdrawal all information regarding that subjected will be deleted and subject files will be placed in approved medical record disposal bins.

Consent Process:

Written informed consent will be obtained for each subject. Consents will be obtained in English; the consenting process can also be given in Spanish by the Study Coordinators, who speak Spanish and can perform the process in Spanish. For Spanish-speaking subjects, a Spanish consent form will be provided. As detailed, research consents will be obtained in the operating room holding area of University of Miami Hospital for patients admitted the day of surgery. In hospital patients will be consented the night prior to surgery in their admitted locations.

Patient's identity and age must be verified prior to obtaining informed consent, as well as his understanding of Risks and benefits and possible alternatives available explained before any informed consent signature from those patients willing to participate. The PI(s) with each study participant will:
• Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study.
• Ensure each patient is notified that they are free to discontinue from the study at any time.
• Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided.
• Ensure each patient provides signed and dated ICF before conducting any procedure specifically for the study.
• Ensure the original, signed ICF(s) is/are stored in the investigator's Study File.
• Ensure a copy of the signed and dated ICF is given to the patient for future reference of the study.
• Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an IEC/IRB.

All potential subjects will be given ample time to review the consent form and discuss any questions and concerns with research personnel or study doctor as well as they will be provided with a copy of the signed ICF. Consent must be documented with a dated signature on the consent form from both the patient and the study personnel conducting the consent discussion.