Does Perioperative Goal Directed Therapy using Flotrac Improve Outcomes in Esophagectomy Patients

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Medical University of South Carolina
Protocol

PI Names: George Guldan, MD

Study Title: **Does Perioperative Goal Directed Therapy using Flotrac Improve Outcomes in Esophagectomy Patients**

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A. SPECIFIC AIMS

The objective of this prospective, randomized controlled study is to ascertain whether the perioperative use of the FloTrac device to guide fluid and vasopressor management during esophagectomy improves patient outcomes. The primary outcome is cardiopulmonary complications; however, the secondary outcome of decreasing patient morbidity (acute renal injury, anastamotic leak, and overall length of both ICU (intensive care unit) and hospital stay.

Hypothesis:
The perioperative use of the FloTrac device will better guide fluid and vasopressor management and result in a decreased incidence of cardiopulmonary complications in Esophagectomy patients as well as decrease other immediate postoperative complications.

B. BACKGROUND AND SIGNIFICANCE

Esophagectomy offers a chance for long-term survival to patients with esophageal cancer. These procedures are often performed on patients with multiple comorbidities and correspondingly have high rates of postoperative complications. Overall mortality rates can approach 8% with high volume centers at rates of 5% (1). The most challenging aspect of the care of these patients is that overall complication rates can be as high as 60% with the majority being cardiopulmonary in origin (2). These surgeries are long, often lasting 6 hours, and are associated with a significant systemic inflammatory response that can lead to significant perioperative hypotension when combined with general anesthesia and thoracic epidural analgesia. This leads to large amounts of fluid administered to treat the hypotension. That, combined with the hypotension and resulting interstitial edema, can lead to conduit hypoperfusion and possible failure. Reviewing our own institutions' data in the STS (Society of Thoracic Surgeon) database revealed a 3 year mortality of 5% with an 8% incidence of anastomotic failure. Morbidity rates, especially pulmonary complications, are common which is consistent with the literature. Intravenous fluid administration is currently the primary mechanism to maintain blood pressure because of the dogma to avoid the use of vasoactive infusions due to the possible negative effect on the conduit. A few animal models have shown that intravenous vasopressor administration (including use of pure alpha agonists such as phenylephrine) decrease blood flow to free musculocutaneous flaps (5-7). This has led to a dogmatic belief that all vasopressors should be avoided intraoperatively during Esophagectomy and other micro vascular surgery, despite there not being any clinical data to support this. However, recent literature shows that both

phenylephrine and epinephrine infusions to treat hypotension increases blood flow to the conduit in Esophagectomy patients (3-4).

Due to prolonged general anesthetics, epidural analgesia and the postoperative SIRS(Systemic Inflammatory Response Syndrome) , these patients often receive large amounts of perioperative crystalloids to maintain normal blood pressures. These patients often have concomitant cardiopulmonary disease, which complicates their treatment and can be a set up for excess fluid administration causing harm. Patients often exhibit intraoperative and post operative hemodynamic lability with periods of hypotension that may not necessarily be related to hypovolemia. Consistently treating periods of hypotension with more intravenous fluids can lead to serious postoperative complications such as graft failure, pulmonary edema, and congestive heart failure. Currently, this patient population at our institution suffers from high rates of pulmonary complications, in particular with many patients having the need for prolonged supplemental oxygen, pneumonia, and intubation for pulmonary edema. This is consistent with the literature and this patient population globally. We believe there is an excellent opportunity to reduce these complications and improve conduit function and ultimately outcomes by implementing a goal directed therapy approach both intraoperatively and postoperatively.

Take note that even a normotensive patient may benefit from modulation of cardiac output if they are overcoming a low output state with self-regulating vascular tone via endogenous vasoconstrictors.

General anesthesia very often ablates this autoregulation, but our protocol hopes to capture every permutation of physiological presentations.

The Edwards FloTrac device is an approved and validated medical device that analyzes the arterial pressure waveform to calculate delta stroke volume based on diastolic filling (intravascular volume status by proxy). This stroke volume variation can be used to better guide intraoperative patient therapy with regard to need for fluid vs.vasopressor management during periods of intraoperative and post operative hypotension (6). Thus, we hypothesize the intraoperative use of the FloTrac device will better guide providers to provide the physiologically necessary therapy for perioperative hypotension, thus improving postoperative outcome. Our primary endpoint is the number of cardiopulmonary complications, with secondary endpoints involving renal injury, anastomotic leak rate, as well as ICU and hospital length of stay.

C. PRELIMINARY STUDIES

Dr. Will Hand (colleague in the MUSC Department of Anesthesia and Perioperative Medicine) recently completed a study in the ENT flap patient population looking at intraoperative GDT's(Goal Directed Therapy) effect on ICU length of stay, flap failure rate, and duration of mechanical ventilation. In this study, ICU length of stay in the GDT group was 33.7h vs 58.3h in the control group, and time on the ventilator also was significantly reduced. There was no increase in flap failures in the treatment group and in fact, there was a trend for improved flap outcome and less reoperation. We believe the current study has similar promise in improving outcomes in a very challenging patient population.

D. RESEARCH DESIGN AND METHODS (including data analysis)

This study will be a prospective, randomized multisite trial evaluating the use of the FloTrac device to guide intraoperative fluid vs. vasopressor management in Esophagectomy at MUSC and Emory.

MUSC will serve as the Lead Site, which encompasses the following responsibilities: developing the protocol, construction of the REDCap database and the analysis of data. Data will be kept for six years and destroyed per MUSC policy. Regulatory oversight at the other sites will be under the purview of their IRB.

Subjects will be randomized into one of two groups by a pre-determined randomization list for each site created by a MUSC statistician. Group one will serve as a control group and will not have a FloTrac device, Group two will have the FloTrac device and the attached algorithm will be used to direct the amount of fluid and vasopressors the participant receives.

Study Description:

The study will be a multi-center randomized controlled trial conducted at 2 sites to evaluate the impact of using the FloTrac device to manage fluid and vasopressor administration during an esophagectomy relative to current standard of care on patient outcomes. The primary outcome of interest is the rate of cadiopulmonary complications. Secondary outcomes include anastomotic leak rate in each patients group, ICU length of stay, hospital length of stay, and acute renal injury. Study participants will be followed until discharge from the hospital.

Selection/Inclusion Criteria:

1. Patients 18 years of age or older
2. Patients undergoing primary resection of esophageal cancer and resultant esophagectomy.

Exclusion Criteria:

1. Patients < 55kg or > 140 kg, based on literature regarding accuracy of FloTrac.
2. Patients with sustained preoperative dysrhythmias, based on literature regarding accuracy of FloTrac (atrial flutter and/or atrial fibrillation).
3. Patients with diagnosed NYHA class III-IV failure or documented EF < 30%
4. Patients who are unable/unwilling to consent for study procedures

PREOPERATIVE (procedures will be consistent across all sites for both groups)

INTRAOP (Items 1-13 are clinical care):

Group 1 Control (no Flotrac):

1. Anesthetic induction based on patient characteristics (awake FOI (fiber optic intubation)vs asleep intubation)-accepted drugs include volatile, propofol, isoflurane, sufentanil, lidocaine, muscle relaxant.
2. Standard lines and monitors as dictated by ASA (American Society of Anesthesiologist): arterial line, large bore IV and CVC prior to incision. 3. Baseline arterial blood gas with long panel, prior to incision.
3. A balanced maintenance anesthetic per anesthesiologist with the goal of stable hemodynamics.
4. One IV to infuse calculated maintenance fluid rate with balanced crystalloid (Plasmalyte or Lactated Ringers (LR) at 1 ml/kg, based on ideal patient body weight, throughout intraoperative procedure.
5. Intraoperative ABG (arterial blood gas) with long panel and BMP (basic metabolic panel) every 3 hours or sooner if deemed necessary by provider (i.e., insulin infusion, multiple transfusions, large acute blood loss, sudden hemodynamic instability, etc) throughout case.
6. Further fluid management as guided by intraoperative hemodynamics (MAP>60), blood loss and UOP (urinary output)at discretion of anesthesia provider.
7. All fluids and (bolus, infusion) will be recorded in real time.
8. Total operative time will be recorded.
9. All blood loss is to be recorded in real time.
10. Patients will be ventilated using pressure regulated volume control mode or pressure control mode with a lung protective strategy of no greater than 6cc/kg and PEEP (positive end expiratory pressure) of 5mmHg (rate determined by practitioner) throughout the case. EtCO2 will be kept at level to ensure a pH of > 7.2 during one lung ventilation and throughout the case. Otherwise, it will be kept near the patient's baseline value for a pH between 7.3-7.4. FiO2(fraction of inspired oxygen) will be titrated to keep sat>97% and PaO2(partial pressure arterial oxygen)>80mmHg on ABG.
11. IVF (intravenous fluids) administered will be standardized as follows: Plasmalyte-A or Lactated ringers will be used for all patients during intraoperative care and CTICU stay. Colloids will not be used, due to endothelial dysfunction in this patient population.
12. Blood transfusions will be administered for Hbg<7gm/dL for normotensive patients not on pressors OR at Hg<8 gm/dl for patients requiring inotropes and pressors. FFP and/or

platelets will be administered based on surgical bleeding and coagulation tests based on current best practices.

13. Patients will be extubated at the end of surgery.

Group two (Arterial line with FloTrac connection)

In addition to the clinical care procedures listed for Group one, the control group, the following algorithm will be employed intraoperatively:

TREATMENT ALGORITHM (See appendix):

The APCO (arterial pressure cardiac output) mode on the Flotrac device is self-calibrating. Will need to enter accurate height, weight, age for each patient (BSA calculated internally).

a. If patient is hypotensive (MAP less than 10% of baseline preoperative blood pressure)

1. First evaluate the delta stroke volume (Delta SV): If delta SV> 10%, give 250 mL IVF challenge. If delta SV is > 10% after 10 minutes, repeat up to 2000 ml.
2. If SVV (stroke volume variation) is < 10%, then evaluate Cardiac Index (CI). Normal CI. If CI <2.2L/min/m2, add inotrope epinephrine infusion at .01mcg/kg/min and reassess in 10 minutes.
3. If CI >2.2L/min/m2, assess Systemic Vascular Resistance (SVR).

If SVR<800, add phenylephrine infusion (initiate 10mcgmin and titrate to effect, max 50 mcg/min).

If SVR <800 and phenylephrine is at the maximum rate, attempt 250 ml fluid bolus and reassess from the beginning of the algorithm.

IF SVR>800, reassess in 10 minutes from beginning of algorithm.

POSTOP:

Both Groups will follow clinical care procedures:

1. All patients should be extubated from the OR.
2. All patients will have Thoracic epidurals managed daily by the Anesthesia Acute pain service. Rate will be adjusted for the minimal rate that provides adequate analgesia.
3. All patients will receive transfusions of PRBC to maintain Hg >7gm/dl. Any patient requiring vasopressors or inotropic support will be kept at a Hg of >8gm/dl.
4. All patients will have ABG's monitored daily while in the ICU to track PaO2/FiO2 ratio.
5. All radiographs will be interpreted by a radiologist blinded to the subject's participation in the study.

Group 1

This group will NOT have FloTrac device in post-op period. Post-op management will be based on institutional standards for this patient population when not otherwise specified.

1. Fluid management:

a. Patients will receive 175ml/hr of Plasmalyte A or Lactated Ringers as maintenance fluid.

b. Patients will receive 500 ml IV bolus of balanced crystalloid for MAP (mean atrial pressure)<60 or UOP less than 30ml/hr. Pt. will be reassessed and bolus will be repeated as clinically indicated.

Group 2
Flotrac Goal Directed Therapy Algorithm will be followed until it is clinically indicated to remove the atrial line.. The arterial line will checked for a quality signal to assure accurate CI and delta SV data. Patients will continue to receive 1ml/kg/hr of Plasmalyte A or LR as maintenance fluid.

Hemodynamic and fluid management will be by perioperative algorithm.(see attached).

1. If patient is hypotensive (MAP less than 10% of baseline preoperative blood pressure)
    a. First evaluate the delta stroke volume (Delta SV): IF delta SV> 10%, give 250 ml IVF challenge.
    If delta SV is > 10% after 10 minutes, repeat up to 2000ml.
    b. If SVV is < 10%, then evaluate Cardiac Index (CI). Normal CI. If CI <2.2L/min/m2, add inotrope epinephrine infusion at .01mcg/kg/min reassess in 10 minutes.
    c. If CI >2.2L/min/m2, assess Systemic Vascular Resistance (SVR). SVR<800, add phenylephrine infusion (initiate 10mcgmin and titrate to effect, max 50 mcg/min).If SVR <800 and phenylephrine is at maximum rate attempt 250 ml fluid bolus and reassess from the beginning of the algorithm. IF SVR>800, reassess in 10 minutes from beginning of algorithm.

DATA TO BE COLLECTED

Primary outcome is number of Cardiopulmonary complications, such as:

- CPR
- reintubation,
- non-invasive ventilation
- defibrillation
- atrial fibrillation
- pulmonary edema (diagnosed via chest x-ray)
- pneumonia (diagnosed via chest x-ray)
- CHF (including diastolic failure):
    - based on Framingham criteria for new onset CHF
    - based on NYHA(New York Heart Association) class

Secondary outcomes:

- Renal injury- based on RIFLE and AKIN guideline
- Serum creatinine of 0.3 mg/dl in 24 hours
- Anastomotic leak (clinical diagnosis on radiograph).
- Death
- Length of hospital stay.
- Length of ICU stay.

Analysis Plan and Sample Size Justification:
The primary hypothesis is that use of the FloTrac will significantly decrease the rate of cardiopulmonary adverse event. Thus we will be comparing the proportion of subjects that experience cardiopulmonary adverse event between the two group using a chi-square test approach and will be conducted based on intention to treat. For the secondary time to event outcomes (hospital and ICU length of stay), we will use a competing risk approach where we will treat death as the competing risk. All other secondary outcomes are categorical and will be evaluated for association with treatment group using chi-square tests or Fisher's exact test when appropriate.

The rate of 50% is the median internationally reported rate of cardio-pulmonary complications (reference is in the Background section of the protocol). We have increase the sample size to 140 patients total (35 at Emory, 105 at MUSC, and 70 per treatment arm) in order to detect a 25% reduction in complication rate which is similar to decreases in complication rates seen in other surgeries where goal directed therapy has been implemented. For example, a reduction of 24% in all major complications in GI surgery was observed when goal directed therapy was used intra-operatively (11). Our patient populations has a higher rate of comorbidities and the current standard of care does not implement goal directed therapy, therefore we fully anticipate to see at least a 25% reduction in complication rates. Additionally, in our study we will implement goal directed therapy both intra-operatively and post-operatively which should result in an even larger reduction in complication rates. Note, we are including 12 more patients that are necessary to power the study (58 patients per group are required for 80% power to see a reduction from 50% to 25%) to account for drop-out.

E.. PROTECTION OF HUMAN SUBJECTS

1. RISKS TO THE SUBJECTS

a. Human Subjects Involvement and Characteristics

Patients enrolled will be those coming for an esophagectomy via the CT (cardiothoracic) surgery service at MUSC. Only patients 18 years of age and older will be offered enrollment into this study. We anticipate more male patients than female, based only on the historical surgical populations, but no bias will be made to enrollment based on sex or race. See table below for anticipated breakdown and total number of patient included based on power analysis based on local historical data for anastomotic leaks and outcomes.

Targeted/Planned Enrollment Table

Total Planned Enrollment :140 at the two sites

Enrolled at MUSC: 105

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	3	9	12
Not Hispanic or Latino	12	81	93
Ethnic Category: Total of All Subjects*	105		
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	0	3	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	27	30
White	12	60	72
Racial Categories: Total of All Subjects*	15	90	105

**The "Ethnic Category: Total of All Subjects" must be equal to the"Racial Categories: Total of All Subjects".*

All eligible participants who volunteer for the study will be enrolled regardless of gender, race, or ethnicity. Every effort will be made to enroll participants from both genders and a variety of racial/ethnic backgrounds. It is difficult to estimate the proportion of gender or ethnicity representation in the study population, as this is a predetermined group of patients who are diagnosed with esophageal cancer and are deemed acceptable candidates for microvascular free tissue transfer.

b. Sources of Materials

Laboratory data will be collected from electronic medical record systems or point of care testing tools; all of the laboratory data collected for the study is standard laboratory values already employed during the intraoperative and postoperative course for these patients. The laboratory data will be available for providers to view and make clinical decisions as they would in non-research patient care.

Postoperative data regarding length of stay, length of days on ventilator, etc will be collected by our research team and/or by chart review.

c. Potential Risks

Enrollment will be voluntary the participant may choose to not participate in the study.

The proposed risk to human subjects is minimal. There is no increased procedural risk involved with using the FloTrac device; all patients undergoing an esophagectomy currently receive an arterial line as standard practice. The FloTrac device attaches to our standard arterial line catheter so the procedure of placing an arterial line is the same for both patient populations. There is literature supporting the use of vasopressor infusions during free flap surgery and esophagectomy, but there are also a small series of publications in animal models demonstrating microvascular vasoconstriction (theoretically making anastomosis more difficult) which has led several surgeons to request no vasopressors be used under any circumstance.(4-8) We hypothesize the use of goal directed therapy using delta stroke volume and the associated calculations will allow superior management of hemodynamic instability and improve surgical conditions, patient tolerance, and ultimately the outcome of the surgery.

There is a risk the monitor could malfunction, if this happens the participant will be withdrawn from the study and he or she will receive standard of care.

There is also the potential risk of patient health information being violated, to avoid this we are using departmental computers (password protected) and CITI trained personnel only to collect and analyze data.

2. ADEQUACY OF PROTECTION AGAINST RISKS

a. Recruitment and Informed Consent

Informed consent will be obtained by the study PI, Co-I's or research staff trained on the protocol either during the patient's preoperative surgical visit or during anesthesia work up on the morning of surgery.

The study, including risks and benefits, will be explained thoroughly to all subjects. Subjects will be informed that study participation is voluntary and will have the opportunity to read the consent document and ask questions.
Informed written consent will be obtained in a private area. All persons obtaining consent will be familiar with the methods and objectives of the study.

Participants will be randomized on the morning of surgery.

b. Protection against Risk

As per the protocol and foreseeable risks described above, hemodynamic perturbations will be treated systematically and if the intravascular volume management/pressor management directed by the study protocol are preventing acceptable patient care, the patient will be withdrawn immediately.

In regard to risks of loss of confidentiality, every effort will be made to protect patients in this regard. HIPAA standards applied, access to data limited to the study team and safety review panel. Data will be stored in secure locations with study-specific numerical identifiers only. All computerized data will be kept within a locked office on the MUSC secure network with password protection. De-identified data will be collected from all sites using REDCap database under password protection and computer encryption.

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

We hypothesize that the use of goal directed management will improve many aspects of patient care. Our primary outcome of cardiopulmonary complications is a major contributor to morbidity in this population(some studies show cardiopulmonary complications at 50%). Tissue edema from excess fluid administration and hypotension from inflammation are key mechanisms in these patients acquiring these complications. We also believe that improvements in ICU length of stay (LOS) will be caused by shortened requirement of ventilator support, fewer cardiovascular complications and less overall physiologic pertubation (e.g. pulmonary edema, kidney dysfunction, and congestive heart failure). The study may improve patient outcome by improving perioperative volume and hemodynamic management . Further, this study will likely identify patient populations who are most likely to benefit from goal directed management.

The potential risks listed above are reasonable in light of the potential benefits for several reasons. There are no new procedural risks and the technology is vetted in literature, and requires only different hardware interface.
Based on several studies, the physiological and surgical risks of using vasopressors are minimal and have repeatedly been shown to be compatible with safe, efficient, and effective microvascular anastomosis. The benefit we hope to achieve of decreasing total fluid and blood administration have been shown to be associated with improved patient and conduit outcomes both locally and at other centers.

4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

Knowledge to be gained from this study is related to optimization of fluid administration/vasopressor use to a proven volume-sensitive surgical population. Within the esophagectomy population, iterations of improvement have occurred; these include implementing early extubation, multimodal analgesia with thoracic epidurals, and early mobilization. The perioperative period has been identified as a critically important time period in terms of ischemic injury, and this study hopes to prove that goal directed hemodynamic control can decrease anastomotic leak and secondary patient comorbidities. If goal directed fluid administration proves effective in shortening ICU length of stay and improving cardiovascular outcomes, these results may be generalizable to this population and other procedures. Regardless of generalizability, there are thousands of patients having esophagectomy surgeries per year that may benefit.

5. SUBJECT SAFETY AND MINIMIZING RISKS (Data and Safety Monitoring Plan)

All data will be kept in a locked office, in a locked cabinet and electronic data will be stored on a password protected MUSC server.

All Protocol Amendments require PRC and IRB approval.

All serious adverse events will be reported to the DSMB and IRB per MUSC policy.

Significant Protocol changes are defined as changes in any of the following: a) Study objectives, b) Research plan or study design, c) Eligibility, d) Statistical Consideration, e) Patient population and/or accrual figures. Any significant change requires PRC approval prior to IRB submission

The DSMB of the Department of Anesthesia and Perioperative Medicine is composed of Drs. Jerry Reves, John Waller, and Fred Guidry. All are full professors at MUSC who have engaged in clinical research throughout their careers.

Data safety and esophageal conduit viability will be analyzed biannually by MUSC's Department of Anesthesiology and Perioperative Medicine's DSMB. Any adverse event will be evaluated immediately and reported to the institution's PRC and IRB to ensure safety of the protocol. Data monitored will include volume and rate of fluid administration, ICU stay duration, myocardial infarctions, failures to extubate, need for blood transfusion, or other sentinel events. The primary endpoint for the study is cardiopulmonary complications. Secondary endpoints will be renal injury, anastomotic leak rate, ICU and hospital length of stay.

On a monthly basis, report updated accrual information to PRC. In addition, PRC conducts a biannual trial performance review in which the level of accrual is reviewed.

F. REFERENCES/LITERATURE CITATIONS

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11. **Cecconi, M. et al. Goal-directed therapy – what is the evidence in surgical patients? The effect on different risk groups. Critical Care 2013; 17: 1-15.**

G. CONSULTANTS

Where applicable, attach electronic versions of appropriate letters from all individuals confirming their roles in the project. Go to the application under "additional uploads" to attach this information.

H. FACILITES AVAILABLE

All data collection and analysis will be performed at MUSC's PACU, Surgery/Trauma ICU, and offices of the Department of Anesthesiology and Perioperative Medicine.

I. INVESTIGATOR BROCHURE

If applicable, attach the electronic version of the investigator brochure. Go to the application under "additional uploads" to attach this information.

J. APPENDIX

algorithm