UF | Institutional Review Board
UNIVERSITY of FLORIDA

Health Center Institutional Review Board
FWA00005790

PO Box 100173
Gainesville FL 32610-0173
Telephone: (352) 273-9600
Facsimile: (352) 273-9614
Email: ufirb-l@lists.ufl.edu

DATE: 6/9/2016

TO: Olga Nin
4440 SW 84th Way
Gainesville, Florida 32608

FROM: Peter Iafrate, Pharm.D
Chair IRB-01

IRB#: **IRB201600185**

TITLE: The prevention of hypotension after epidural analgesia after major surgery by adding epinephrine to infusions to counteract sympathectomy: a double- blind, controlled, randomized, prospective dose-finding study

Approved by Full Board (Contingencies Met)	**Expires on:**

The Full Board voted to approve this study with contingencies on 4/20/2016. The requested contingencies were addressed by the PI and approved by a designated reviewer on 6/8/2016.

Approval Includes, but is not limited to:

Protocol PI Version dated 05/23/2016 V3

Dated and watermarked IRB-approved Informed Consent Form PI Version dated 6/6/2016

Principal Investigator Responsibilities:

The PI is responsible for the conduct of the study. Please review these responsibilities described at: http://irb.ufl.edu/irb01/researcher-information/researcherresponsibilities.html
Important responsibilities described at the above link include:

- Using currently approved consent form to enroll subjects (if applicable)
- Renewing your study before expiration
- Obtaining approval for revisions before implementation
- Reporting Adverse Events
- Retention of Research Records
- Obtaining approval to conduct research at the VA
- Notifying other parties about this project's approval status

Study Team:

Keith	Thompson	Co-Investigator
Paul	Crispen	Co-Investigator
Hari	Parvataneni	Co-Investigator
Andrew	Gifford	Other
Terrie	Vasilopoulos	Co-Investigator
Chris	Giordano	Co-Investigator

Anna	Woods	Study Coordinator
Judith	Wishin	Other
Steven	Hughes	Co-Investigator
Andre	Boezaart	Co-Investigator

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Protocol

1. Project Title

The prevention of hypotension after epidural analgesia after major surgery by adding epinephrine to infusions to counteract sympathectomy: a double- blind, controlled, randomized, prospective dose-finding study

Date: 02/15/2016
03/29/2016

2. Investigator(s):

Olga C. Nin, MD (Principle Investigator)
Andre P. Boezaart, MD, PhD (Co-Investigator)
Christopher Giordano, MD (Co-Investigator)
Steven J. Hughes, MD (Co-Investigator)
Hari K Parvataneni, MD (Co-Investigator)
Paul L Crispen (Co-Investigator)
Keith Thompson, MD (Co-Investigator)
Terrie Vasilopoulos, PhD (Co-Investigator)
Anna Woods, RN (Study Coordinator)

3. Abstract:

Epidural analgesia via continuous epidurally infused local anesthetic agent (LA) is widely and very successfully used routinely for perioperative pain control in patients undergoing major orthopaedic and abdominal surgery since 1928[1] and also at the University of Florida (UF). The routine practice of the UF Acute Pain Service (APS) is to use either ropivacaine 0.2% without any additives at a continuous infusion rate of 8 mL per hour and a patient-controlled bolus injection of 4 mL, which is locked out at 60 minutes intervals, or the above with 5 mcg per mL of epinephrine added to the ropivacaine. The choice currently depends on the preference of the APS physician in charge of the case. A frequent unwanted side effect of epidural block is hypotension due to the epidurally injected LA blocking the sympathetic nerves and thus the patient's

response to hypotension, which is usually due to hypovolemia and/or an unopposed parasympathetic (*via* the vagus nerve) nervous system. A sympathetic block, inhibits the cardiovascular system and the adrenal cortexes from responding appropriately by releasing catecholamines which normally mitigate hypotension from any cause. This sympathelytic blockade is exacerbated by an unopposed parasympathetic tone that decreases cardiac output by decreasing contractility and heart rate as well as leading to more vasodilatation.

Epinephrine is a mixed alpha- and beta-adrenergic receptor agonist. It has alpha 1 and 2 as well as beta 1 and 2 agonistic properties. It thus increases the total peripheral vascular resistance by arteriolar and venous vasoconstriction, which increases venous return to heart and thereby cardiac preload. It also increases the inotropic, chronotropic and lusitropic qualities of the heart through its beta-1 effects, which lead to a greater cardiac output. And these same beta-1 agonist effects simultaneously increase spinal cord and cerebral blood flow.

The addition of epinephrine to epidural solutions, which has been in use for many years, has been widely studied and found to be safe. For example, Niemi et al studied epidural solutions that either contained ropivacaine, fentanyl, with 2mcg/mL epinephrine or the same solution without the epinephrine. Niemi demonstrated that the solution with epinephrine added improved analgesia, reduced side effects, and facilitated earlier mobilization without adding any risk.[2]

The aim of this study will be to study the hemodynamic effect(s) of adding epinephrine to the local anesthetic solution and to find its optimal concentration to counteract the sympathectomy.

4. Background:

The beneficial role of epidural anesthesia in surgical practice has been well documented. Apart from the humanitarian aspects of effectively treating pain and suffering, other advantages have been widely studied. For example, in a large

retrospective meta-analysis in 2003, the benefits of epidural analgesia included reduced perioperative cardiac morbidity (~50%), pulmonary infections (~40%), pulmonary embolism (~50%), ileus (~2 days), acute renal failure (~30%), and blood loss (~30%).[3] The Multicenter Australian Study of Epidural Anesthesia (MASTER) study was another landmark paper in which the authors showed a substantial benefit regarding improved analgesia, reduced respiratory failure, and with minimal risk adverse consequences.[4] Epidural analgesia has also been shown to increase gastric motility by blocking thoracolumbar sympathetic flow, reducing postoperative use of opiates and increasing gastrointestinal blood flow.[5,6].

A limiting factor in the use of epidural analgesia, however, is the high incidence of associated hypotension. Hypotension is defined as systolic blood pressure (SBP) > 20% below the baseline preoperative measurements and acquired before the epidural or any sedation has been administered. Effective segmental epidural block would thus invariably cause sympathectomy due to its location in the thoracic or lumbar areas by blocking the cardiac sympathetic nerves, the pre-ganglionic nerves to the adrenal glands or the sympathetic nerves to the blood vessels individually or in combination.

It has been proven beyond doubt that epinephrine, when added to ropivacaine 0.2% and used for epidural analgesia by infusion, is safe and may even improve spinal cord blood flow and the analgesic effects of ropivacaine.[7] It is also known that the cause of hypotension associated with epidural analgesia is the blockade of the sympathetic outflow to the cardiovascular and adrenal systems, and that the ideal mechanism to counter this would be by beta1-stimulation, which is ideally achieved with low-dose epinephrine.

Finally, it is known that epidural infused epinephrine increases its serum concentration.[8] What is not known is whether added epinephrine will counteract this sympathetic blockade and prevent hypotension, and what the optimal concentration of epinephrine infusion would be during epidural analgesia with 0.2% ropivacaine to achieve optimal analgesia and optimal hemodynamic status.

5. Specific Aims:

We aim to examine whether adding epinephrine will counteract the sympathetic blockade and prevent hypotension, and what the optimal concentration of epinephrine infusion would be during epidural analgesia with 0.2% ropivacaine that can achieve both optimal analgesia and optimal hemodynamics. Specifically we plan to answer the following questions:

1. Does the addition of epinephrine to the epidural infusion of 0.2% ropivacaine:
    a. Prevent hypotension?
    b. Lead to a wider spread of local anesthetic effect?
    c. Lead to a difference in the average pain scores?
    d. Lead to a difference in when ambulation occurs?
    e. Decrease potential of other opioid-related side effects such as pruritus, nausea/vomiting, respiratory depression and opioid consumption?
2. What is the optimal concentration of epinephrine (2mcg/mL or 5mcg/mL) to achieving the above-mentioned outcomes?

6. Research Plan:

Activity	*Screen*	*Pre-op (baseline)*	*Pre-op after epidural, before bolus*	*Pre-op after epidural, after bolus/before anesthesia*	*Intra-op*	*Post-op Recovery (PACU)*	*1 hour post-op*	*Transfer to floor*	*POD 1*	*POD 2*	*POD 3*
Informed consent	X										
Inclusion / Exclusion Criteria	X										
Medical History	X										
Randomization		X									
IV Placement		X									
Primary measurements(SBP,DBP,MAP, HR,SaO2,RR,Pain score?) every 3-5 min		X	X	X	X						
Epidural Placement		X									
Administration of Pre-op sedation			X								
Prep and supply of test drug			X								
Infusion of Study drug if randomized for test group				X							
Infusion of Ropivacaine				X							
Primary measurements every 15 min						X	X				
(Secondary measurements) Sensory block assessment (1 hour post-op and every 6 hours for the subsequent 72 hours						X	X		X	X	X
Intra-op surgical records					X						
Anesthesia Pain Service records			X	X	X	X	X	X	X	X	X
Pain Scores DVPRS Score							X		X	X	X
Record 24 hour I/Os						X			X	X	X
Pain management and "Rescue Drug" administration as needed							X	X	X	X	X
Record opioid usage						X	X	X	X	X	X
All SOC points and monitors: EKG, non-invasive BP; ETCO2; pulse ox; arterial line with Flow Track (if indicated); peripheral or central venous line; induction and mode of anesthesia.		X									
Physical therapy rehabilitation records (Time and distance of ambulation)									X	X	X

Patients will be approached about their willingness to participate in this study either in a pre-operative surgical or anesthetic clinic visit or in the pre-operative area on the day of surgery. Consent will be obtained by a member of the research team. The patient will be given time to read the consent, have all study related questions answered, and discuss the study with their family, if desired. A copy of the signed consent will be placed in the patient's physical chart, and a research progress note documenting study enrollment will be made in the patient's electronic medical record.

Inclusion criteria:

Up to 250 patients between the ages of 18 and 80 years undergoing epidural analgesia to treat perioperative pain associated with major surgery will be approached for their willingness to participate in the study. Patients undergoing major thoracic, abdominal, urological or orthopaedic surgery for whom thoracic or lumbar epidural block would be indicated and planned for intraoperative and postoperative analgesia as per the UF Acute Pain Service (APS) usual and routine practice will be included in this study. Our epidural failure rate is lower than 20% and our institution performs around 100 epidurals a month. If only a 1/3 of our patients agree to be part of our study we would have 24 study patients a month. This would then mean that our study would take 10 months to complete data collection.

Exclusion criteria:

Sepsis (febrile, above normal and upward trending white blood count, and/or positive cultures for systemic infection), patients with acute trauma, coagulopathy [INR >1.4, platelets < 100,000, and/or anticoagulation medication given out of UF APS adaptation of the American Society of Regional Anesthesiologists (ASRA) guidelines[9] , preoperative hemodynamic instability, symptomatic coronary artery disease (angina etc.), patients from the ICU whose tracheas were intubated for any cause, patient refusal, pregnancy, allergies to medications in the protocol, and primary or secondary block failure.

Standard of Care - Preoperative Period:

All patients will receive a standardized continuous epidural block at the appropriate level for the planned surgery by the APS physician staffing the block room that day. For the standardized continuous epidural block, placement will be confirmed with loss of resistance technique (LORA), wave form analysis or nerve stimulation. .

Patients will receive a bolus of 500 mL of 5% Albumin intravenous infusion as per the usual routine practice of the APS before the main bolus dose is injected. A preoperative level of block will be established that is appropriate for the surgery by injecting an appropriate volume of ropivacaine 0.5% or lidocaine 2% w/ epinephrine 1:200,000 (5–10 mL) into the epidural space as per the usual practice of the APS. This will be done after the routine test dosing with 3 mL of 2% lidocaine and 1:200,000 epinephrine, confirmed that intrathecal and intravascular markers are negative. If an insensate-to-cold area in the appropriate dermatomes cannot be established within 10 minutes following a 5 to 10 mL (maximum 10 mL) injection of ropivacaine 0.5%, the epidural catheter will be removed and replaced. If this process is repeated and there was still no level, it will be annotated and the patient will be removed from the study, labeled as a primary block failure, and treated appropriately by the attending anesthesiologist by either repeating the epidural block placement a third time or using other appropriate perioperative analgesia.

Research-Related Procedures - Preoperative Period:

Once consent is obtained, patients will be randomly allocated by computer-generated randomization to one of four groups. This will be a quintuple blinded prospective study. The anesthesiologist managing the intraoperative anesthesia, the anesthesiologists (APS) placing the blocks and following the patients on the floors, the research nurse taking the measurement, the surgeons, nor the patients will be aware of what combination of drugs are used for the epidural block infusion.

The three groups will consist of:

1. Group A (Ropivacaine 0.2% infusion; Control group)
2. Group B (Ropivacaine 0.2% + 2 mcg/mL epinephrine)

3. Group C (Ropivacaine 0.2% + 5 mcg/mL epinephrine)

The pharmacists will make up and supply test drugs for groups A, B and C and provide them labeled to the block area drug dispenser as “A, B, or C test solutions” without specifically identifying the content.

Immediately following the establishment of an appropriate level for the planned surgery, an infusion of the test drug will be initiated at 4 to 8 mL per hour with a 4- to 8-mL patient-initiated bolus at a lockout interval of 1 hour – typically 8 mL per hour for major abdominal or thoracic surgery and thoracic epidural placement and 4 mL per hour for hip arthroplasty and lumbar epidural. Once established as effective for the clinical situation, this infusion will be left unchanged throughout the surgery and postoperative period. If clinically indicated, and the infusion rate is changed above these limits, the patient will be removed from the study. If the infusion is changed to below the limits of 4 – 8 mL per hour, this indicates the end of the need for the epidural infusion or otherwise untreatable hypotension.

Standard of Care - Intraoperative and Postoperative Periods:

Intraoperative and postoperative fluid management will be at the discretion of the anesthesia and primary teams.

Preoperative sedation will be a maximum of 5 mg of midazolam by intravenous injection (IV) and alfentanil 2000 mcg IV. Monitors include: EKG, non-invasive blood pressure, ETCO2, pulse oximeter, arterial line with Flow-Track (if indicated and appropriate per intra- or postoperative operative anesthesiologist), peripheral intravenous or central venous line as deemed appropriate by the attending intra- or postoperative operative anesthesiologist. Induction of anesthesia and mode of anesthesia (maintenance, fluid management, intraoperative analgesia, muscle relaxation, etc., are at the discretion of the attending intraoperative anesthesiologists.

If hypotension (see definition below) is encountered intraoperatively, the attending anesthesiologist will start a vasoactive or positive inotropic medication as indicated by the patient's medical requirements.

Research-Related Procedures – Intraoperative:

- Anesthesiologists will be encouraged to use alpha agonists if the other causes of hypotension are excluded and lumbar epidural is judged to be a contributory cause of the hypotension; and epinephrine, dobutamine, or dopamine (or indirect inotropic agents such as ephedrine) if thoracic epidural is judged to be the cause of the hypotension and the other causes of hypotension such as hypovolemia have been ruled out.
- The epidural infusion will be continued intraoperatively at a rate 4 to 8 mL per hour. Emergence medications will be administered and recorded as judged appropriate by the intraoperative anesthesiologist. A bolus of 5 mL of ropivacaine 0.5% without additives may be administered through the epidural catheter at the conclusion of the intraoperative phase by the intraoperative anesthesiologist or APS anesthesiologist in the recovery room, if required.
- "Rescue" drugs as outlined below will be administered and recorded if deemed necessary. If, after sensation level testing, the epidural block was not appropriately covering the area of surgery, a further bolus of 5 mL of 0.5% ropivacaine will be injected by the APS physician and if this was still not managing the pain, this will be noted and the patient will be removed from the study. If judged appropriate by the APS physician, the epidural will either be replaced in the recovery area or the "rescue" medication described below will be initiated.
- Hypotension is defined as SBP > 20% below the baseline in the block room area before the epidural or sedation for the epidural was administered or an MAP less than 55 mmHg. Epidurals will be turned down or turned off if the treating Intensive Care Primary Physician declared it an emergency, if the patient had hemodynamic instability stemming from other causes that was complicated by the sympathetic block of the epidural, or significant hypotension, or mean MAP <

30%, from baseline and other causes such as hypovolemia had been corrected. If this is the case, the patient will be removed from the study.

Research-Related Procedures - Postoperative Periods:

If additional pain management or "rescue" analgesics are needed, for example, from outside the area covered by the epidural; subjects may receive any of the following:

- Acetaminophen (Tylenol) 1000 mg scheduled intravenously every 8 hours for the first 48 hours and, after oral intake is restarted, it will be changed to 1 gram every 6 hours by mouth (patients with liver disease will be excluded if appropriate and after discussion with the hepatic surgeon)
- Ketorolac Tromethamine (Toradol) 30 to 60 mg every 6 hours intravenously
- Celecoxib (Celebrex) 100 mg per mouth every 12 hours
- Oxycodone 5 to 10 mg per mouth every 4 hours as needed
- Intravenous hydromorphone (Dilaudid) patient-controlled analgesia (PCA) as per APS routine protocol appropriate for age and body habitus of the patient.

Primary measurements:

Include the average invasively or non-invasively measured SBP, diastolic blood pressure (DBP), MAP, arterial blood oxygen saturation (SaO2), heart rate, respiratory rate, and pain by the visual analog pain score (VAS) on the "Defense and Veterans Pain Rating Scale" (DVPRS) measured over the following set periods:

<u>Preoperative period</u>

Primary measurements every 3 to 5 minutes and at indicated time points:

I. Before the bolus epidural is injected.
II. After the epidural bolus is injected but before anesthesia is induced.

<u>Intraoperative period</u>

Primary measurements every 3 to 5 minutes

<u>Postoperative period</u>

I. Primary measurements in the recovery room (if appropriate) every 15 minutes

II. Primary measurements following transfer to the floor every 4-6 hours if within normal limits, but every hour if needed for closer observation in case of possible abnormality for as long as the epidural analgesic blocks are continued, but at least every 8 hours after discharge from the PACU.

Secondary measurements:

III. Spread of block per spinal root segment as tested by sensitivity to cold recorded every hour postoperatively and every 8 hours for the subsequent 72 hours after discharge from the PACU.

IV. Ambulation on the first day after surgery (POD 1), POD 2 and 3, will be recorded per physical therapy protocol and distance ambulated per 24-hour period will also be recorded. Physical Therapy information will be gathered to test motor effect on lumbar epidurals.

V. Opioid usage data will be recorded and converted to morphine equivalents and averaged for POD 0, 1, 2, and 3 per group.

VI. Side effects such as pruritus, nausea/vomiting, and respiratory depression (defined as respiratory rate less than 10 breaths per minute of oxygen saturation more than 7 points lower that the patients preoperative value on room air) will be recorded and managed as deemed appropriate by the attending physician.

VII. 24 hour I/O for the first 72 hours to assess fluid balance, length of stay, and amount of days before return to PO status.

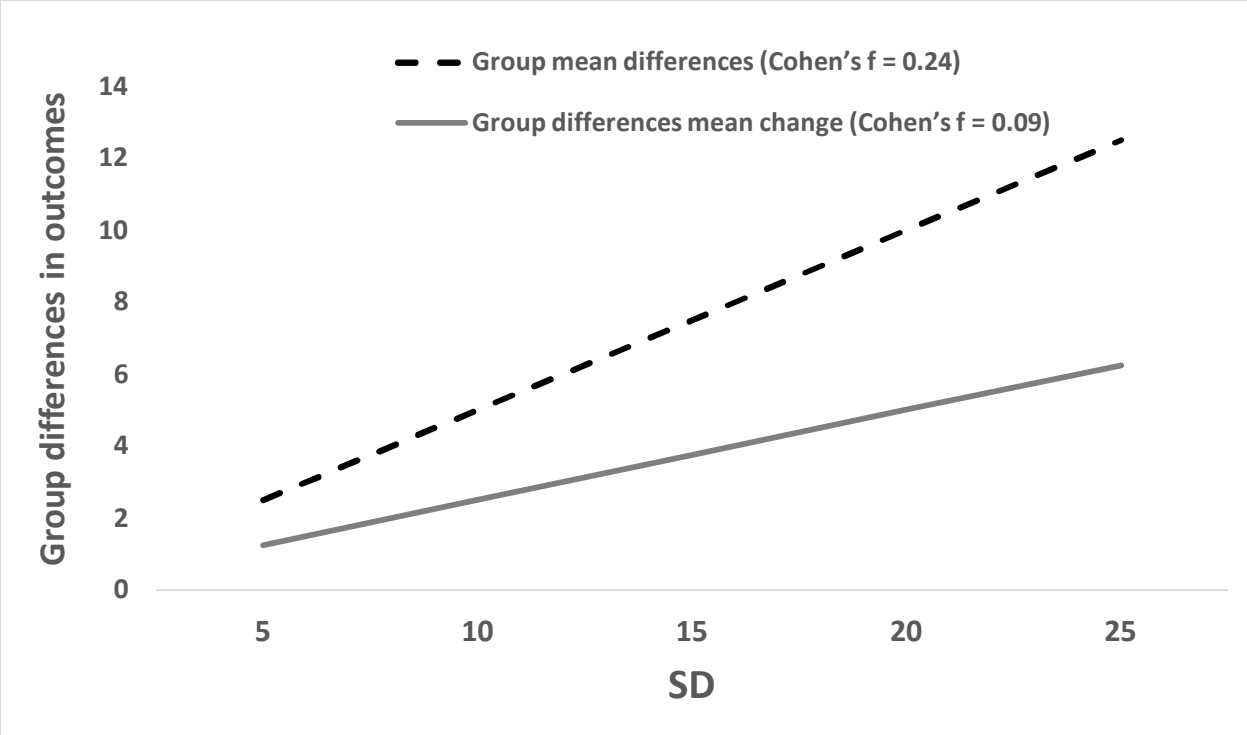
Data analysis plan

All data will be entered securely using the online database or Red Cap. To assess potential dose-response effects on changes in continuously measured primary outcomes, repeated measures mixed modeling analyses will be used. This type of analysis can assess the main effects of time (i.e., change) and group (i.e., epinephrine dose; coded as an ordinal variable) on the outcomes. Mixed models are the preferred approach to analyze data with repeated measures; these models can account for

correlation among repeated measurements, flexible time effects, and can handle missing data. Additionally, this model can estimate time × group interactions. If this interaction is statistically significant, that provides evidence that the changes in outcomes are different depending on the dose of epinephrine that a patient received. Logistic regression models will be used to assess the relationship between epinephrine dose and incidence of hypotension (SBP < 20% or MAP < 55 mmHg) and other categorical outcome variables. A P value of <0.05 was considered statistically significant for all statistical tests. All analyses were conducted in JMP Pro 11.0 (SAS Institute, Cary, NC).

Sample size determination

At 80% power (alpha = 0.05), a sample of n=200 (50 per group) will be able to detect 26% differences in incidence of categorical outcomes, and an effect size of Cohen's f = 0.24 for group mean differences and effect size of Cohen's f = 0.09 for group differences mean change over time. Figure 1 depicts how these effect sizes will translate to the outcomes, with assumed standard deviations in outcomes ranging from 5 to 25. For example, assuming MAP has an SD = 10, the present study will be able to detect mean differences of 5 mmHg across groups and group differences of 3 mmHg for mean change over time.



ADMINISTRATIVE RESPONSIBILITIES:

Study Resources: The principal investigator will oversee the data collection, data analysis and will maintain the records in confidence. Should any evidence suggest that the study protocol require modification, the PI will notify the IRB in a timely manner for review and approval. Each subject will be identified by number, not by name, on all data forms. To protect confidentiality, all data will be numerically coded and information linking the numeric codes to individual participant's names will be kept in a locked file in the PI's office.

7. Possible Discomforts and Risks:

Regional anesthesia - The risks of regional anesthesia include, but are not limited to low blood pressure, allergic reaction to drugs, obstruction or cessation of breathing, headache, paralysis, nerve injury, bleeding, blood clots, infection or meningitis, falls after surgery, drug reactions (including rash, shock, and cardiac/respiratory arrest), stroke or brain injury, heart failure or heart attack, and death.

The epidural would be immediately turned off if the patient were to have unwanted side effects such as uncontrolled increase in heart rate or blood pressure, arrhythmias, anxiety, or unwanted clinical symptoms that could be attributed to the epinephrine dose in the epidural. The pharmacy would immediately be contacted to determine the epinephrine dose in the patient's epidural so that clinical treatment be tailored appropriately.

The PI will oversee the data collection, data analysis, and will maintain the records in confidence. The data collected will be stored in a secure, password protected database with strong encryption, on a computer server, accessible only by the study team. Any additional digital data files from the study will be de-identified and stored on a password protected laptop computer. Hence, encryption will be required. All paper records will be stored in locked file cabinet in the PI's locked office. The patient consent forms will be the only documentation with PHI. The results collected and calculated by the laptop software will be non-PHI data including the patient demographics, administration amounts of drugs, the time of those administrations, and the post-operative times to emergence and the occurrence of respiratory depression.

8. Possible Benefits:

It has been proven beyond doubt that epinephrine, when added to ropivacaine 0.2% and used for epidural analgesia by infusion, is safe and may even improve spinal cord blood flow and the analgesic effects of ropivacaine.[7] Because of this, the possible benefit to the participant is to improve the effects of the epidural anesthesia and to reduce the possible sympathetic side effects.

9. Conflict of Interest:

None of the investigators have a conflict of interest.

References

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