Erector Spinae Plane Block for Uncomplicated Renal Colic

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Erector Spinae Plane Block for Uncomplicated Renal Colic

Short Title: ESPB for Kidney Stones

Protocol Version 1.3

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1 ABBREVIATIONS

ECRF – Electronic case report form
ED – Emergency department
EHR – Electronic health record
EP – Emergency physician
ESP – Erector spinae plane
ESPB – Erector spinae plane block
G6PD – Glucose-6-phosphate dehydrogenase deficiency
HIPAA – Health insurance portability and accountability act
POCUS – Point of care ultrasound
U-M – University of Michigan
US – Ultrasound
UGRA – Ultrasound guided regional anesthesia

2 STUDY SUMMARY

2.1 Title

Erector spinae plane block for renal colic

2.2 Primary Objective

Determine the efficacy of the erector spinae plane block (ESPB) performed by emergency physicians (EPs) for the treatment of pain related to uncomplicated urolithiasis

2.3 Secondary Objectives

- Determine the effect of ESPB on emergency department (ED) operations metrics (disposition, length of stay, return to ED)
- Determine the effect of ESPB on use of opioid medications in the ED and during the follow up period
- Estimate rate of complications for ESPB when performed by EPs

2.4 Hypothesis

EP performed ESPB will reduce the proportion of patients receiving a second parenteral medication to treat pain in the ED

2.5 Study Design

Single site two-stage open label phase 2 clinical trial with one treatment arm and one external control arm

2.6 Inclusion Criteria

- Adult emergency department patient presenting with pain due to uncomplicated urolithiasis
- Imaging confirmation of urolithiasis on the index encounter or prior encounter within 7 days
- Patient received one dose of parenteral pain medication in the ED

2.7 Exclusion Criteria

- Pregnancy or breastfeeding
- Prisoner or incarcerated individual
- Therapeutic anticoagulation or coagulopathy
- Active treatment for urinary tract infection (either acute infection or chronic therapy)
- Prior spinal surgery in the thoracic region
- Allergy to local anesthetic
- Soft tissue infection overlying the injection site
- Covid positive
- Inability to communicate verbally or read/write in English
- Currently taking strong CYP1A2 inhibitor (fluvoxamine, amiodarone, fluoroquinolones, etc.)
- Glucose-6-phosphate dehydrogenase deficiency (G6PD)

2.8 Primary outcome

Proportion of patients that receive a second parenteral medication for pain related to urolithiasis

2.9 Secondary and exploratory outcomes

- Difference in visual analog scale pain (1-10) from prior to procedure to first pain assessment after 60 minutes from completion of ESPB as assessed by bedside nurse

- ED operational metrics – admission to hospital, rate of 72-hour return to ED and length of stay
- Opioid pain medication usage measured in intravenous morphine equivalents and proportion of patients that receive a prescription for opioid pain medication
- Survey follow-up administered online with/without telephone assistance at 1, 7 and 30 days from initial ED visit (days 1, 7 are optional and on day 30 pain medication use questions are optional)
- Frequency of prespecified complications related to ESPB

2.10 Sample Size

- This study is a two-stage trial with one planned interim analysis for futility
- Based on the prior 30-month time period (as of May 2022), 572 out of 1071 patients (53.4%) presenting to the ED and meeting the inclusion criteria did not require a 2nd parenteral pain medication during the ED encounter. Thus, we estimate a baseline response rate of 55%.
- Prior work by Nobel et al.[1]and Aydin et al.[2] suggests that no patient will require a second dose of any pain medication after ESPB, but we estimate a conservative response rate of 75% for treatment with ESPB.
- Using Simon's optimal two-stage design[3] with these parameters and $\alpha = 0.05$, $\beta = 0.10$, we estimate that 18 subjects will be required at the interim analysis and 54 subjects will be required to complete this study.
- Using a Bayesian two-stage design, where interim analysis is planned at one-third total enrollment and a stopping rule if there is only a 10% probability of ESPB demonstrating a 75% response rate, we estimate that 45 total subjects (15 at interim analysis) will be required to achieve a 1.4% chance of stopping early and 95.2% chance of rejecting the null hypothesis.[4,5]
- This study will aim to achieve a total enrollment of 60 subjects who receive ESPB to account for losses to follow up and withdrawals from the study. Up to 180 (3:1 ratio) historical controls will also be included in the study thus the total enrollment including both treatment and control patients is 240.

3 STUDY DESCRIPTION

3.1 Background

Urolithiasis (kidney stones) affects 1 in 11 people in the United States[6] and pain caused by urolithiasis is a common cause for presentation to the ED in the United States, totaling more than 1 million visits per year.[7] Additionally, up to one in ten patients who present to the ED for kidney stones return to the ED for reevaluation and as many as a third of these patients require admission to the hospital.[8] While complications of kidney stones may necessitate treatment with antibiotics, procedural interventions and admission to the hospital, the vast majority of both the initial and repeat ED visits are due to uncontrolled pain but are unlikely to result in procedural intervention[6]. Often, uncontrolled pain may be accompanied with nausea which limits the ability of patients to utilize oral medications both in the ED and at home leading to the frequent need for parenteral medications, commonly opioids and non-steroidal anti-inflammatory medications, to break the cycle of severe pain caused by kidney stones. At U-M, our preliminary data (Appendix Table 1) demonstrates that approximately 50% of patients receive 2 or more doses of parenteral medications to treat kidney stone related pain in the ED. Nationally, diagnosis of kidney stones has been associated with long term opioid use[9] and opioid medications are often prescribed after ED visits related to kidney stones.[10,11] Recent efforts to reduce opioid use and prescribing in the ED[10,12] has led clinicians to seek alternative therapies to treat severe and refractory pain including the use of regional anesthesia.[1,2]

3.2 Erector spinae plane block for urolithiasis

The ESPB was first described in 2017 and has gained popularity for its utility as a safe and effective pain control modality for a variety of surgical procedures including abdominal, breast, thoracic and lumbar spine surgery[13–16]. The ESPB provides analgesia by inhibiting neurotransmission at the dorsal and ventral rami of the thoracic spinal nerves, providing anesthesia to multiple dermatomal levels.[17] The ESPB is especially suited for renal colic because epidural spread has also been noted for local anesthetic agents leading to both visceral and somatic analgesia.[18] The technique has been shown effective for treating the pain associated with percutaneous nephrolithotomy as well.[19] The procedure has also been adopted in the Emergency Department for treating pain from rib and spinous process fractures, herpes zoster, and acute pancreatitis.[20–24] Recent case series described use of the ESPB for treatment of renal colic. Aydin et al. performed a pilot randomized trial of 40 patients evaluating ESPB performed by emergency physicians against non-steroidal anti-inflammatory drugs for renal colic and found that patients in the ESPB group had significantly lower opioid consumption and pain scores measured on a visual analog scale.[2] Of note, patients receiving ESPB in this study had no opioid medication use after the procedure. Likewise, Noble et al. reported a case series of 10 patients whose renal colic was treated with ESPB and concluded that within 30 minutes of the procedure, most patients had total or significant reduction in their pain and that the ESPB was effective in those patients with opioid use disorder.[1] Importantly, in both these studies, no significant complications of the procedure were reported.

3.3 Ultrasound guided regional anesthesia in the ED

Ultrasound-guided regional anesthesia (UGRA) encompasses a variety of procedures that can be used in the Emergency Department for treatment of pain and to facilitate procedures.[25] UGRA utilizes real time guidance of anesthetic injection near a target nerve or in the desired fascial plane to cause sensory blockade.[26] UGRA offers effective pain control without the side effects and potential long term abuse potential of opioids.[25] The best studied UGRA plane block technique in in emergency medicine is the fascia iliaca block for treatment of hip fracture related pain.[27] Multiple randomized trials have demonstrated the fascia iliaca block is not only safe and effective for treating pain, but also prevents complicating pneumonia in elderly hip fracture patients and improves functional outcomes.[28,29] The serratus anterior plane block is another widely used UGRA technique for the treatment of rib fractures in the ED with both demonstrated efficacy and an excellent safety profile.[30–32] The ESPB is a similar plane block technique, that has the potential to benefit patients with a variety of painful conditions of the trunk.

3.4 Summary of Rationale

- Kidney stones are a common reason for emergency department visits
- Pain related to kidney stones can be incredibly painful and refractory pain may lead to increased use of parenteral medications in the ED as well as increased opioid prescribing
- ESPB is a common plane block utilized by EPs to treat pain with an excellent efficacy and safety profile

3.5 Study Aims

- Determine the efficacy of the erector spinae plane block performed by emergency physicians for the treatment of pain related to uncomplicated urolithiasis
- Determine the effect of ESPB on ED operations metrics (disposition, length of stay, return to ED)
- Determine the effect of ESPB on use of opioid medications in the ED and during the follow up period

- Estimate rate of complications for ESPB when performed by EPs

3.6 Outcomes

3.6.1 Primary Outcome and rationale

The primary outcome will be the proportion of patients receiving a second parenteral pain medication in the ED after a single-shot ESPB is performed by a study investigator. We have reviewed historical data that suggests that the rate of response (percentage of patients that do not require a second parenteral pain medication) in patients with urolithiasis, and who receive a parenteral medication as the first analgesic in the ED (approximately 70% of all kidney stone patients), ranges from 47 to 57% for the years 2020 – 2022. The average response rate is 53.4% during this period which is in line with historical trends prior to the Covid-19 pandemic.

3.6.2 Secondary Outcomes

- Difference in visual analog scale pain (1-10) from prior to procedure to first pain assessment after 60 minutes from completion of ESPB assessed by bedside nurse
    - Historic data from the U-M ED suggests that the median maximal pain reduction (last pain score minus first) in the ED is a mean reduction of 3.4 points (SD = 3.0) from a starting value of 7.9.
- ED operational quality metrics:
    - Rate of admission to hospital
    - Rate of 72-hour return to the ED
    - ED length of stay
- Safety outcomes and complications at day 30

3.6.3 Exploratory Outcomes

- Difference in highest and lowest pain scores while patient is in the ED
- Opioid pain medication usage measured in intravenous morphine equivalents and proportion of patients that receive a prescription for opioid pain medication
- Immediate complications of ESPB
- Survey follow-up administered online with/without telephone assistance at 1, 7 and 30 days from initial ED visit assessing the following outcomes:
    - Duration of pain control after ESPB (day 1 survey only)
    - Delayed complications of ESPB (optional except for day 30)
    - Patient satisfaction with pain control and procedure
    - Use of opioid and other pain medication after discharge from the index ED visit

4 STUDY POPULATION AND ENROLLMENT

4.1 Target Population

Our target population is patients who present to the U-M Adult ED with flank or back pain due to uncomplicated urolithiasis (see also appendix figure 1A).

4.2 Inclusion Criteria

- Adult (>18 years) emergency department patient presenting with pain due to uncomplicated urolithiasis
- Imaging confirmation of urolithiasis on the index encounter or prior encounter within 7 days
- Patient received one dose of parenteral pain medication in the ED

Rationale for inclusion criteria: We seek to enroll adult patients who have pain that initially required parenteral medications to treat and thus, may benefit from adjunct therapy to treat severe kidney stone related pain.

4.3 Exclusion Criteria

- Pregnancy or breastfeeding
- Prisoner or incarcerated individual
- Therapeutic anticoagulation or coagulopathy.
- Active treatment for urinary tract infection (either acute infection or chronic therapy)
- Prior spinal surgery in the thoracic region
- Allergy to local anesthetic or prior local anesthetic systemic toxicity
- Covid positive
- Inability to communicate verbally or read/write in English
- Currently taking strong CYP1A2 inhibitor (fluvoxamine, amiodarone, fluoroquinolones, etc.)
- Glucose-6-phosphate dehydrogenase deficiency

Rationale for exclusion criteria: Pregnant patients are especially at risk for complications of urolithiasis as are patients with active treatment for acute UTI or chronic suppressive therapy and will be excluded from this study. Long-acting local anesthetics (Ropivacaine) has not been well studied in lactating patients or infants and thus patients who are actively breastfeeding will be excluded. Prior spinal surgery in the anatomic region of the ESPB may distort anatomy and increase risks of performing this procedure. Patients with prior local anesthetic toxicity or allergy to local anesthetics will also be excluded. Patients who cannot communicate in English will be excluded due to difficulty in obtaining informed consent and difficulty following instructions during positioning for the procedure. Covid-19 positive patients will be excluded for infection prevention and safety of study team members. CYP1A2 strong inhibitors such as fluvoxamine, fluoroquinolones or amiodarone can lead to delayed metabolism of ropivacaine. Finally, patients with G6PD may develop methemoglobinemia after administration of local anesthetics.

4.4 Selection of external control patients

External control patients will be selected from a population of patients meeting the following criteria: 1) adult ED patient with the diagnosis of uncomplicated kidney stones; 2) received at least one dose of parenteral medication while in the ED; 3) presentation to the ED between 7/1/2021 and the study start date. From this population, propensity score matched control patients will be selected at a ratio of 3 controls to 1 ESPB patient. External control population patients are not active patients in this study and analysis of their data will be secondary use of data collected during routine care. To provide valid comparison between control patients and ESPB patients, we will compare pain scores obtained by the treatment team (bedside nurse). For all other primary and secondary outcomes, data collection utilizes EHR query that does not require prospective data collection. Please see the data collection section of this protocol for further details.

4.5 Minorities, women, and other vulnerable populations or groups

No groups of patients will be specifically excluded except for those with clinical reasons as stated in the exclusion criteria. No patients will be included or excluded based on gender, age, race, or ethnicity.

4.6 Screening

- Study team members will screen for patients using the ED track board and other patient lists/reports within MiChart (EPIC EHR)
- Study team members will review potential subjects' presenting symptoms, prior medical history, and imaging findings
- Study team members will then notify a physician investigator on call of potential subjects currently in the ED
- Physician investigator will review inclusion and exclusion criteria with other study team members (if they did not perform screening personally) as well as the potential subject

4.7 Informed Consent

- Written informed consent will be obtained by physician investigators prior to any study procedures are performed
- To limit the possibility of coercion during the consent process, the physician investigator (proceduralist) may not be a member of the primary treatment team in the ED and the primary treatment team will be instructed not to recommend participation in the research study
- A copy of the signed consent document will be provided to the participant, an electronic copy will be uploaded to the study database and a paper original will be stored in a secure location
- For external control patients, a waiver of informed consent will be obtained

5 STUDY PROCEDURES

5.1 Study Design and Workflow

This study is designed to be a pragmatic, single treatment arm two-stage trial that investigates the efficacy of the ESPB to treat pain related to kidney stones in ED patients in comparison to an external control group. The overall study workflow is diagrammed in Figure 1B and Figure 1C. We plan to have our study team members screen for patients based on the availability of the ED ultrasound team - a clinical care team that performs diagnostic and ultrasound guided procedures at the bedside in the ED. Eligible patients will be approached by a study investigator (the proceduralist) who will obtain informed consent and perform the ESPB. The investigator will also collect data from the patient 1 hour after performing the procedure. Follow up assessments using a web-based survey are an optional sub-study. Participants who do not elect to participate in the optional sub-study will receive a telephone call at day 30 to assess only for adverse events. Study participation will be complete after final follow up assessment.

5.2 Pre-procedure preparation and safety screen

The proceduralist will explain the ESPB to the patient and answer all questions while obtaining informed consent. After this, the proceduralist and assistants will obtain all nerve block supplies, a department ultrasound system, and properly position the patient. The proceduralist will also ensure that appropriate monitoring equipment (telemetry and pulse oximetry) is in place, primary provider team and primary beside nurse are informed of the procedure, and local anesthetic is obtained from the ED pharmacy. The proceduralist will calculate the maximum safe dose of local anesthetic for the patient. The long-acting local anesthetic to be used in this study is 0.5% Ropivacaine (5 mg/mL) for which the maximum safe dose is 3 mg/kg in 8 hours. The dose will be calculated based on patient weight with a maximum dose of 150 mg (30 mL). Peripheral nerve block is considered on-label use of ropivacaine and the study dose (up to 150 mg) and volume (30 mL) are within the suggested ranges of the approved label.[33] The proceduralist will also confirm the patient does not have allergy to local anesthetic. The proceduralist will also ensure availability of lipid emulsion (Intralipid) in the ED pharmacy. Intralipid is a medication used to treat local anesthetic systemic toxicity (LAST) and would only

be administered in the event of development of LAST. A study team member other than the proceduralist (coordinator or other investigator) will perform a pre-procedure assessment of pain using the visual analog scale. All pre-procedure preparation elements, assessment of pain, and re-confirmation of eligibility criteria will be recorded as the safety screen checklist in the REDCap database.

5.3 Erector spinae plane block

The ESPB is a peripheral nerve plane block routinely performed by emergency physicians for a variety of painful conditions and has been previously described in detail[24,34]. This plane block will be performed as a "single-shot" using a long-acting local anesthetic. Briefly, a timeout will be performed, the correct patient identification, indication, procedure, and laterality will be confirmed. The proceduralist will review the maximum safe dose of local anesthetic and draw up 30 mL of 0.5% ropivacaine (150 mg) into a sterile syringe. No adjunct medications will be used. If the patient's calculated maximum safe dose results in a volume of less than 30 mL, the maximum safe dose will be diluted in sterile normal saline to achieve 30 mL total volume. With the patient in the sitting, decubitus or prone position per the patient's preference, ultrasound will be used to identify the transverse spinous process at the level of T8 and this site will be marked. The injection site and technique have all been previously used in a clinical trial for the same indication.[2] A hair covering, mask, eye protection and sterile gloves will be donned. The site will be cleaned with chlorhexidine solution and allowed to fully dry. ESPB will be performed with sterile technique using in-plane ultrasound guidance. After administration of local anesthetic, the proceduralist will clean the site and apply a bandage. The proceduralist will document a research visit note in the EHR that indicates time the ESPB was performed, immediate complications, recommended actions if complication, and contact information for the study team.

5.4 Post-procedure assessment

Immediately after the procedure, the proceduralist will assess for immediate complications with the patient and inform the primary care team as well as the patient of the expected time course for effective analgesia. At one hour after the procedure, a study team member other than the proceduralist will reassess pain with the patient using the visual analog scale. The study team will also inquire as to preferences for follow up assessment (if the participant has opted in). These data will be recorded into the electronic case report form (ECRF) as the post-procedure assessment.

5.5 Post-emergency department follow up

Follow up assessments will be performed at 1-, 7- and 30-days post emergency department visit. The goal of these brief assessments is to collect data regarding: 1) quality and duration of analgesia related to ESPB; 2) use of other medications for pain and nausea; 3) further treatments and healthcare utilization for kidney stones. Participants in follow up assessments will be compensated with $10 Amazon.com gift cards or equivalent compensation delivered electronically for each completed assessment which we estimate will take 5-10 minutes or less to complete.

For participants who receive ESPB but do not elect to participate in the optional follow-up, the study team will call the participant at day 30 and assess only for potential adverse events related to ESPB. Participants who did not consent for the optional follow-up will not be asked about pain medication usage, return visits to the ED and other information unrelated to adverse events.

6 DATA COLLECTION

6.1 Summary of Data Management

Data collection will occur at three stages: 1) primary data collection by the study team during the index ED visit; 2) follow-up data collection at 1-, 7- and 30-days post-ED visit; 3) secondary data collection using EHR query and, if needed, manual chart review. All data will be centrally stored in REDCap. Access to the study REDCap database will be made available only to study team members.

6.2 Primary data collection during index ED visit

A study team member (coordinator or other investigator) other than the proceduralist performing the ESPB will assess pain prior to and 1 hour after the procedure. Prior history of kidney stones and urologic procedures will be collected. A safety screen will also be performed prior to procedure by the proceduralist. Data entry into REDCap will occur via electronic case reporting form.

6.3 Follow up assessments via web-based survey

At day 1, 7 and 30 after the ED visit, a brief web-based survey will be administered to the participant via E-mail with or without telephone assistance based on the participant's preference. This survey form will assess pain management after the index ED visit, return visits to the ED, and other outpatient follow up or interventions for kidney stones. Each follow up assessment will also evaluate for known complications of ESPB and other adverse events. All follow up assessments are part of the optional sub-study optional except for the assessment of adverse events at day 30.

6.4 Secondary data collection from the EHR

Variables regarding patient demographics, ED operations metrics, diagnoses, medical history, procedures performed, other healthcare encounters, nurse assessments of pain, medications administered, and prescriptions provided during the index ED visit will be obtained using direct query to the EHR databases (RDW, HSDW, Caboodle, Clarity) and confirmed with manual chart review if needed. Using the same EHR query we will also collect data regarding historical control patients (external controls that did not receive ESPB). Control patient data will be collected as secondary data collection of routinely collected health information.

6.5 Data storage

All data used in this study will be centrally stored in REDCap. This study is anticipated to take up to 2 years to complete. The REDCap database will be placed into archive mode and stored for 7 years after this point for recordkeeping purposes.

7 DATA ANALYSIS PLAN

7.1 Descriptive analysis and statistical testing

The primary exposure of interest is performance of ESPB for uncomplicated renal colic in the ED. We will describe the center and spread for all collected variables. Additionally, we will compare data from participants to historical control patients whose data is collected secondarily from query to the EHR. Continuous variables will be described by medians with interquartile ranges and differences will be assessed by two-sample t-test or Wilcoxon's rank sum test depending on distribution. Categorical variables will be described by counts with proportions and differences assessed using the Chi-squared test or Fisher's exact test where appropriate. An alpha = 0.05 will be considered the level of significance in all analyses.

7.2 Primary analysis

Our primary analysis will evaluate the proportion of patients receiving ESPB who require a second parenteral pain medication. This outcome will be compared to external control patients who are selected using propensity score matching at a ratio of 3:1. The propensity score model will include the following variables: age, gender, triage acuity level (ESI score), first ED pain score assessed by nursing, Charlson Comorbidity Index, chronic and initial pain medication type. Data for this outcome will be collected via EHR query as above.

7.3 Interim analysis

Both a Simon's optimal two-stage and Bayesian two-stage design were used to estimate sample size (see section 2.10 above) with the Simon's design yielding a slightly larger group for interim analysis (18 patients). Thus, we will plan to perform an interim analysis at 18 recruited patients who have received the ESPB and if 8 or more patients receive a second parenteral pain medication then the study will be ended for futility.

7.4 Other outcomes

Other outcomes unique to study patients (received ESPB as part of this study) including change in pain score, follow up assessment outcomes, complications, and patient satisfaction will be analyzed before-after the ESPB, change over time, or descriptively as appropriate. Secondary outcomes derived from EHR query (ED operations metrics, opioid medication usage and prescriptions) will be analyzed for study patients in comparison to external controls. All comparisons to external control patients will be made using data collected via EHR query rather than prospectively collected data (investigator collected pain scores, patient satisfaction, follow survey results, etc.) which will be reported descriptively and without comparison to controls.

8 RISK ASSESSMENT

8.1 Potential Risk to Subjects

This study is a single treatment arm trial of ESPB for uncomplicated renal colic to investigate efficacy and complications. Prior studies did not report any major or minor complications as a result of ESPB performed by emergency physicians. However, in prior studies performed perioperatively by anesthesiologists, the following complications were identified: local anesthetic toxicity or allergy, infection or bleeding of the soft tissue overlying the needle insertion site, vascular puncture, pneumothorax, and failed block. Based on prior literature, complications are considered extremely rare because the potential space superficial to the T8 transverse process (site of injection to create plane block) is far from the spinal cord, pleura and major blood vessels. Additional risks to participants include risk of delay in care or other analgesia medication as well as temporary discomfort (lasting less than 1 hour) due to the procedure. Additional risks to both participants and external controls (whose data is secondarily collected from EHR query) are loss of confidentiality.

8.2 Minimization of procedure related risk

To minimize risk from ESPB, the proceduralist will perform a safety screen during the pre-procedure preparation. This safety screen data will be collected and monitored by the study team. The safety screen is in addition to a timeout which will be conducted immediately prior to the procedure and will include confirmation of the correct patient identification, indication, procedure, and laterality. Immediately post-ESPB, the proceduralist will monitor the patient for complications and reassess for pain at 60 minutes. The proceduralist will document a research visit note in the EHR that indicates time the ESPB was performed, immediate complications, recommended actions if complication, and contact information for the study team.

8.3 Minimization of confidentiality risk

To minimize the risk of breach of confidentiality to participants and external control patients, the highest levels of data security will be maintained. Central data collection will be performed using REDCap, a secure, HIPAA compliant encrypted database. Both primary (collected by study investigators directly into ECRF) and secondary data collection (EHR query) will utilized REDCap for secure storage of data. Only study team members will be granted access to REDCap which is login and password protected.

8.4 Potential Benefits

Participants in this study may receive improved pain control as prior evidence suggests near complete resolution of renal colic pain with ESPB. Additionally, participants in the study may receive less total exposure to other pain medication and may have improvement in nausea, vomiting, and length of stay in the ED. External control patients will not benefit from this study but future kidney stone patients may benefit from the knowledge gained.

8.5 Risk Relative to Benefit

There are two levels of risk in this study.

1) For patients in the intervention (ESPB) arm: Prior studies have demonstrated an exceptionally safe risk profile for ESPB. Thus, risks relative to benefits are considered to be a *minor increase over minimal risk*. Minor, temporary discomfort at the needle insertion site due to the procedure is expected to last only minutes and not more than 1 hour.
2) For patients in the historical external control group: The primary risk is breach of confidentiality and is *no more than minimal risk*.

8.6 Data and Safety Monitoring Plan

8.6.1 Human Subjects Involvement

This study will involve emergency department adult patients at U-M who meet the inclusion and exclusion criteria. The target number of subjects in the proposed study is based on sample size estimates performed with assumptions from preexisting clinical studies and preliminary data from U-M.

8.6.2 Data sources and data collection

Study participants will have data primarily collected during the index ED visit and up to 3 follow-up, web-based assessments. These data will be stored and directly collected into REDCap ECRFs. This study also secondarily uses data collected during routine care including administrative and EHR data. All available data sources will be utilized to monitor for adverse events. Additionally, participants will be provided with contact instructions to self-report adverse events. No additional patient contact and no additional primary data collection is required for external control patients.

Data collection for the monitoring of adverse events will be performed by physician investigators during the index ED visit and may also be performed by other study team members during the follow up period. If participants opt-out of the follow up study, any adverse events will be ascertained by secondary data collection from the EHR.

The PI and study coordinator will monitor enrollment and assess for adverse events during at least monthly data review. Data review may occur more frequently based on study enrollment.

8.6.3 Adverse Events

The following serious adverse events (SAE) have been predefined: 1) death as a result of procedure complication; 2) hospitalization or prolongation of hospitalization as a result of

procedure complication; 3) permanent neurovascular injury; 4) pleural or vascular injury requiring surgical intervention; 5) infection at site of procedure; 6) development of anaphylaxis or local anesthetic systemic toxicity after procedure. There may be other unanticipated adverse events which include potential adverse events related to ropivacaine administration These adverse events are listed in Table 3A of the ropivacaine package insert. Please note that the AEs listed here are for regional anesthesia when performed in the intra- and peri-operative settings and with continuous infusion rather than single-shot administration.

All adverse events that occur will be logged centrally and reported to the IRB.

The PI or other study team member will promptly report the following events to the IRB if the events occur within 30 days of participation in the study: 1) any change in the study taken without prior IRB review; 2) interim findings that indicate an unexpected change to the risks or potential benefits of the research; 3) publications that indicate an unexpected change to the risks or potential benefits of the research; 4) serious adverse event as listed above.

Annual reports will be submitted to the local IRB if needed. Reports will contain a summary of all adverse events that occurred since the last IRB review.

8.6.4 Adverse Event Reporting to Medical Team

The PI and physician co-investigators will be responsible for reporting adverse events during the index ED encounter to the primary medical team. The study team member will first notify the covering attending physician either directly or via page/secure MiChart message of the research related adverse event. The study team member will recommend next steps for evaluation and management based on their medical judgement. The physician investigator will also document a research visit note regarding the adverse event, the attending notified, and recommended next steps.

After the index encounter, during the follow up period, the study team member (either physician investigator or non-physician investigator) will notify the PI or designee (other study Co-I and physician) of the discovery of an adverse event. The adverse event will be verified by the PI or designee and the participants primary medical team (if admitted to the hospital) or PCP (if discharged after index visit) will be notified via telephone. Additionally, a research visit note will be documented at this time.

8.6.5 Adverse Event Reporting to the Participant

The PI or designee will notify the patient of adverse event (if not already informed of this) and recommend a next course of action and determine if further medical evaluation is needed. The PI or designee will also document notification of the participant in the research visit note.

8.6.6 Grading, relatedness, and expectedness

The PI or designee will grade each adverse event using a 0 through 5 scale with the following grades:

0 - No adverse event
1 - Mild AE – No treatment needed
2 - Moderate AE – Resolved with treatment
3 - Severe AE – Inability to carry on normal activities, required professional medical attention
4 - Life-threatening or disabling AE
5 - Fatal AE

The PI or designee will also determine the relatedness of any adverse events to study procedures using the following scale:

Definitely related
Probably related
Possibly related
Unlikely to be related
Definitely not related

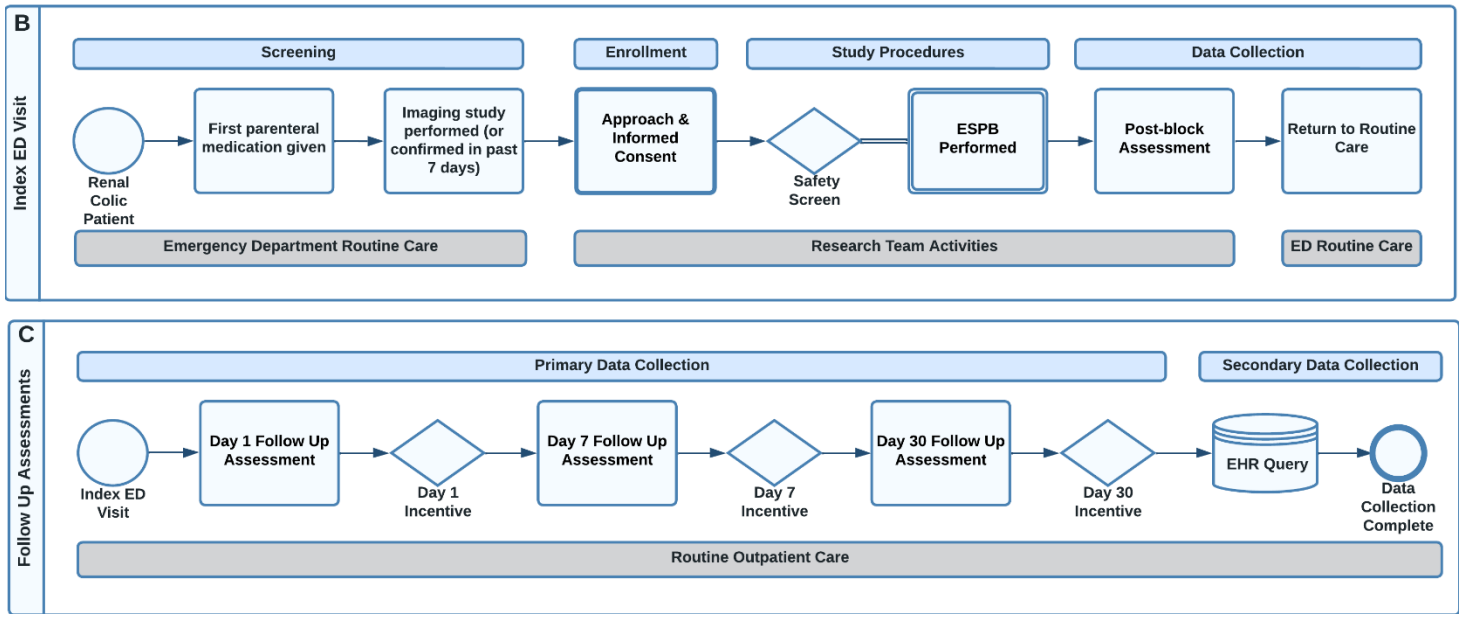
The PI or designee will also determine the expectedness of any adverse events to study procedures using the following criteria:

Unexpected adverse events (i.e., has NOT been addressed or described in one or more of the following: Informed consent document(s) for this study, IRB application for this study, grant application or study agreement, protocol or procedures for this study, investigators' brochure or equivalent (for FDA regulated drugs or devices), DSMB/DSC Reports, published literature, other documentation)

Expected adverse events (i.e., has been addressed or described in one or more of the following: Informed consent document(s) for this study, IRB application for this study, grant application or study agreement, protocol or procedures for this study, investigators' brochure or equivalent (for FDA regulated drugs or devices), DSMB/DSC Reports, published literature, other documentation, or characteristics of the study population)

APPENDIX

Figure 1. Study eligibility criteria and workflow. B) Study workflow during the index ED visit. C) Study workflow during the follow up period.



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