JHM IRB - eForm A – Protocol

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1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Trans-incisional Rectus Sheath Block versus Laparoscopic Guided Rectus Sheath Block for Pediatric Single Incision Laparoscopic Cholecystectomy: A Prospective, Randomized Study

Background: Regional anesthesia has been increasingly utilized for providing post-operative analgesia for a number of surgical procedures in children. Rectus sheath block and local anesthetic infiltration of the surgical site are two common modes for providing post-operative analgesia. Studies comparing the two modes have shown ultrasound-guided rectus sheath block to improve immediate pain scores and reduce use of post-operative analgesia in pediatric patients undergoing umbilical hernia repair. However, these studies have compared pre-incisional ultrasound-guided rectus sheath block to post-operative local anesthetic infiltration as a subcutaneous and/or intradermal injection. Also, to our knowledge, there are no studies evaluating the use or efficacy of laparoscopic guided rectus sheath block for pediatric single-incision laparoscopic surgery. Single-incision surgery involves performing abdominal operations though a single, small incision, usually located at the umbilicus.

Hypothesis: The purpose of our study is to compare the efficacy of trans-incisional rectus sheath block to intra-operative infiltration of the rectus sheath under direct laparoscopic visualization via an intra-abdominal approach for providing post-operative analgesia following single-incision laparoscopic cholecystectomy (SILC) in children.

Methods: We propose a prospective study where pediatric patients who are undergoing single-incision laparoscopic cholecystectomy will be randomized pre-operatively to receive either a trans-incisional rectus sheath block after facial closure but prior to skin closure or intra-operative infiltration of the rectus sheath under direct laparoscopic visualization after cholecystectomy. The primary outcome is the post-operative pain rating based on the Wong-Baker Faces Pain Rating Scale (WBFPRS) following SILC. Additional outcomes measured will include: operative times, the use of intravenous/oral opioid and/or non-opioid medication in the post-operative period, duration of analgesia following surgery based on time to first rescue analgesic, intra-operative hemodynamic changes, post-operative hemodynamic changes, incidence of side-effects, and complications.

Patients/patient guardians will receive a sheet to document post-operative WBFPRS scores, oral opioid and non-opioid medication administration once discharged to home for a total of 5 days.

2. Objectives (include all primary and secondary objectives)

-Primary outcome: Degree of analgesia in the post-operative period following single-incision cholecystectomy

-This will be measured by the Wong-Baker Faces Pain Rating Scale, use of intravenous/oral opioid and/or non-opioid medication in the post-operative period following single-incision cholecystectomy

-**Secondary outcome**: Operative times (this will include into operating room, surgical start, surgical stop, and out of operating room times which will include time required for administration of rectal sheath block or local infiltration), duration of analgesia following surgery based on time to first rescue analgesic, intra-operative vital signs, incidence of side-effects

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Regional anesthetic techniques are commonly used to improve post-operative analgesia in pediatric patients. There continues to be an increase in the use of regional anesthetic techniques in an effort to reduce post-operative pain while limiting the use of opioid medications. Studies have reported improved analgesia when comparing regional anesthetic techniques with intravenous opioids. Some of the regional blocks that have been described in children include: transverse abdominis, ilioinguinal/iliohypogastric nerve, rectus sheath, lumbar plexus, paravertebral and intercostal nerve block. These have been described for use in a number of different surgical procedures in children (1,2).

A few studies have been published comparing bilateral rectus sheath block (RSB) to infiltration of local anesthetic for children undergoing umbilical hernia repair (3-5). One recent prospective, randomized controlled study demonstrated that ultrasound guided rectus sheath block provided superior analgesia in the peri-operative period compared with infiltration of the surgical site after umbilical hernia repair. In this study, the RSB was placed prior to incision, while the local anesthetic infiltration was placed into the subcutaneous tissues after the procedure and prior to closer of the skin incision (3). A second prospective, randomized study also reported decreased use of opioid and non-opioid medications post-operatively for patients who underwent ultrasound guided RSB. In this study, the RSB was placed at the conclusion of the surgery rather than prior to the incision (4). A third randomized, blinded study comparing wound infiltration with ultrasound guided RSB placed prior to incision for umbilical hernia repair demonstrated more effective analgesia in the RSB group (5). The available literature therefore demonstrates the

efficacy and safety of rectus sheath blocks for providing analgesia following umbilical hernia repair.

Single-incision laparoscopic cholecystectomy (SILC) involves performing abdominal operations though a single, small umbilical incision (6). Local anesthetic infiltration of the surgical site is the most common mode for providing post-operative analgesia following SILC. This can be performed prior to the incision or after the operation and prior to closure of the skin incision. To our knowledge, there are no studies to date evaluating the use or efficacy of intra-operative, laparoscopic guided rectus sheath block for post-operative pain control in pediatric patients undergoing SILC. One recently published study evaluating transverse abdominis plane (TAP) blocks placed under laparoscopic guidance at the end of colorectal operations found that using TAP blocks facilitated shorter length of stay with low re-admission and reoperation rates (7). Given that the rectus sheath block provides analgesia along the midline of the anterior abdominal wall, and has been shown to be effective and safe in patient undergoing umbilical hernia repair, we propose a randomized controlled study to compare trans-incisional rectus sheath block to intra-operative infiltration of the rectus sheath under direct laparoscopic visualization/guidance via an intra-abdominal approach for providing post-operative analgesia following single-incision laparoscopic cholecystectomy (SILC) in children.

The majority of regional anesthesia in pediatric patients is performed under deep sedation or general anesthesia. Safety studies support the rationale that performing regional anesthesia under general anesthesia is safe (1). The Pediatric Regional Anesthesia Network (PRAN) was formed to obtain highly audited data on practice patterns and complications in regional anesthetic techniques in pediatric patients. It is a centralized database, at a number of participating centers, and includes a total of 14,917 regional blocks performed on 13,725 patients over a 3 year period. They concluded that regional anesthesia in children as commonly performed in the United States has a very low rate of complications. There were no adverse events reported for the 294 rectus sheath blocks performed (1).

Ropivacaine is a long-acting local anesthetic that has been shown to cause less cardiovascular changes than other local anesthetics (8,9). The overall incidence of adverse events associated with ropivacaine appears to be low with nausea and/or vomiting occurring most frequently (9). It has been shown to be effective for peripheral nerve, caudal, and lumbar/thoracic epidural blocks and produces less motor blockade than bupivacaine after caudal administration (8,9).

With regards to measurement of pain intensity post-operatively, self-reported measures of pain are preferred over other types of pain measures for use with children capable of verbal communications (10). Pain is a subjective experience, and self-report measures ask the patient to articulate their pain experience. This approach also has a high clinical utility as it is convenient and easy to use in every day practice. The Wong-Baker Faces Pain Rating Scale (WBFPRS) is the current standard for measuring pain at our institution. The intended age group range is 3-18 years,

which includes our proposed study population. Advantages of the WBFPRS include: ease of use, minimal instruction required for use, preferred by children of all ages and nurses, and is available free of charge. Studies have reported that the scale has adequate psychometric properties (10). Psychometric properties of outcome measures include level of measurement, reliability, validity, and responsiveness. One study evaluating validity, discriminant validity, and test-retest reliability of the Wong-Baker Faces Scale demonstrated that it is a valid and reliable tool when used to assess procedural pain among verbal children aged 4-18 years and among 3 year olds who can count and understand the instrument (11). A systematic review of the psychometric properties, interpretability and feasibility of self-report pain intensity measure in children and adolescents showed the WBFPRS to be psychometrically strong. They reported advantages of the scale to include: ease of administration, cost effectiveness, and child preference (12).

4. Study Procedures

a. Study design, including the sequence and timing of study procedures

This is a prospective, double-blinded, randomized controlled study comparing the efficacy of trans-incisional rectus sheath block to intra-operative infiltration of the rectus sheath under direct laparoscopic visualization via an intra-abdominal approach after removal of the gallbladder for providing post-operative analgesia following single-incision laparoscopic cholecystectomy in children.

Patients aged 10-21 years old undergoing SILC for cholelithiasis, choledocholithiasis, gallstone pancreatitis, cholecystitis or biliary dyskinesia will be screen for study inclusion. Eligible patients and their parents/guardians will be approached and, if agreeable, consented for the study pre-operatively. Patients will be randomized to receive either trans-incisional rectus sheath block or intra-operative anesthetic infiltration of the rectus sheath under direct laparoscopic visualization by the surgeon after gallbladder removal. Patient, patient guardians, select research team members, and Post Anesthesia Care Unit (PACU) staff will be blinded to the method of analgesic administration.

Standard anesthetic technique: All patients will undergo the standard of care per Johns Hopkins All Children's Hospital (JHACH) Anesthesia Department with regards to the administration of anesthesia for single incision laparoscopic cholecystectomy. Standard vital signs will be monitored by the anesthesiologist or anesthetist throughout the surgical procedure. Acetaminophen 15 mg/kg solution or 325mg – 650 mg oral tab may be given in the pre-anesthesia unit prior to SILC and, when given, will be administered based on patient age and weight. General anesthesia is induced via a mask with Sevoflurane, oxygen, nitrous, and/or propofol or rocuronium IV if the patient has an IV in place. The type of induction anesthesia given will be at the discretion of the attending pediatric anesthesiologist. The airway is then secured with endotracheal intubation. A peripheral IV is placed if the patient does not already have one in place. A volatile inhalational anesthetic is used for maintenance of anesthesia. The patient is monitored for hemodynamic changes throughout the surgical procedure and treated

accordingly. Any changes in hemodynamics or requirements of additional anesthetic or analgesic will be documented and assessed. Hemodynamic changes (>20% increase in non-invasive systolic blood pressure and heart rate after incision) is treated with deepening of the anesthetic with volatile agents. Patients with persistent tachycardia or hypertension are treated with 1mcg/kg of fentanyl. Patients may receive 0.1 mg/kg of ondansetron intravenous or dexamethasone or glycopyrrolate if appropriate and at the discretion of the attending anesthesiologist. If approved by the attending general surgeon, they may also receive 0.5 mg/kg of ketorolac intravenous at the end of the procedure.

Study anesthetic technique: Patients will be randomized into two groups: trans-incisional rectus sheath block or intra-operative infiltration of the rectus sheath under direct laparoscopic visualization via an intra-abdominal approach.

-Trans-incisional rectus sheath block group: After removal of the gallbladder, a predetermined volume of 0.2% ropivacaine (1cc/kg, max dose 10cc, divided into equal doses bilaterally) will be administered under direct visualization into the rectus sheath bilaterally by the attending surgeon. This will be done after closure of the fascial incision but prior to closure of the skin incision.

-Intra-operative rectus sheath block group: After removal of the gallbladder, a predetermined volume of 0.2% ropivacaine (1cc/kg, max dose 10cc, divided into equal doses bilaterally) will be administered intra-abdominally under direct laparoscopic visualization into the rectus sheath bilaterally by the attending surgeon.

Surgical procedure: Patients will undergo single incision laparoscopic cholecystectomy per the standard surgical protocol followed by two attending surgeons at JHACH. The surgical technique for single incision laparoscopic cholecystectomy, including incision closure is standardized, and has been previously published by our pediatric surgery group. Surgical dressings will be standardized for both groups.

Post-operative period: All patients will receive standard post-operative PACU monitoring, including pulse oximeter, non-invasive blood pressure, temperature, and respiratory frequency for phase one and two recovery per JHACH PACU protocol. The PACU team and select members of the research team will be blinded to the method of administration of analgesic. Initial post-operative pain will be assessed by a blinded member of the research team or PACU nurse using the Wong-Baker Faces Pain Rating Scale (see figure below). This is a horizontal scale of 6 hand-drawn faces scored from 0-10. WBFPRS values will be assessed and documented approximately every 10 minutes for 60 minutes and approximately every 30 minutes thereafter for three hours or until discharged home or transferred to the floor. The timing of the recorded pain scale will be at the discretion of the PACU nurse and/or research team member. A time lapse until the next pain

score is recorded will not be considered a protocol violation as the clinical situation may deem a pain score unnecessary (e.g. the patient is asleep/resting quietly). In the PACU, patients with a pain score of ≥ 4 will be given Fentanyl 0.5 mcg/kg every 10 minutes for a maximum of two doses and 0.05 mg/kg of intravenous Morphine every 10 minutes for pain score ≥ 4 thereafter, for a maximum of two doses. Once patients are able to tolerate oral intake, they will be given one or two tabs of oxycodone 5 mg tablet or oxycodone elixir 0.1 mg/kg for one dose for pain score ≥ 4 based on age and weight. The order in which the above mentioned analgesic medications are administered will be at the discretion of the PACU nurses under the supervision of the attending anesthesiologist. The protocol allows that not every pain score ≥ 4 will necessarily be followed by administration of analgesic medication, as the particular clinical scenario may dictate otherwise. Therefore instances in which a pain score ≥ 4 are not followed by administration of analgesic medication will not be considered a protocol deviation. The administration of analgesic medications in the PACU will ultimately be at the discretion of the PACU nurses under the supervision of the attending anesthesiologist, with the above mentioned protocol as a guide.

The WBFPRS values, total amount and type of analgesic administered, time to first rescue medication administered, any supplemental antiemetic or antipruritic medications administered, and any changes in hemodynamics will be assessed and documented. The incidence of nausea, vomiting, and pruritis will be recorded. Patients will be discharged once the standard discharge criteria are met. All patients will be given the standard discharge instructions for SILC and asked to follow up in 2 weeks for routine post-operative visit. If discharge criteria are not met post-operatively patients will be admitted for further management.

Patients admitted to the hospital postoperatively will receive 0.05mg/kg of IV morphine until tolerating PO. Once tolerating PO, oral analgesics will be administered as described below. Pain scores will be recorded approximately every four hours until discharge home. Pain scores will be directly obtained and recorded by the study team during the initial postoperative period in the PACU. If a study team member is not available to remain with the patient for the duration of the recovery period in the PACU, or if the patient is admitted to the floor, the electronic medical record will be the source of data pertaining to pain scores and analgesic administration for the remainder of the patient's hospital stay.

After discharge from PACU or hospital: A WBFPRS sheet will be given to each patient/parent or guardian prior to discharge. They will receive specific instructions for interpretation of the WBFPRS and when to administer oral analgesics. Patients will receive a prescription for acetaminophen-hydrocodone 325/5 mg tablet or acetaminophen-hydrocodone 325/5 mg/15mL elixir, 0.1-0.2 mg/kg for analgesia prior to discharge based on age and weight. Instructions will include checking the WBFPRS value every 4 hours while awake and for a value of ≥ 4 administer the appropriate pain medication as prescribed. Patients will also be instructed to alternate narcotic pain medication with ibuprofen 10 mg/kg every 6 hours while awake for 2 days. They will be instructed to transition to non-opioid analgesic (acetaminophen) once their pain is reported as a

value of < 4. We will instruct patient/patient family to fill out the WBFPRS value sheet, being careful to document WBFPRS values every 4 hours while awake and any administration of analgesics/pain medication for a total of 5 days. We will also provide an area on the value sheet to provide information regarding any post-operative complications/symptoms or concerns. We will provide a self-addressed, stamped envelope so this sheet may be returned to our surgical group via mail. Patients will receive a telephone call from one of the study team members 1 day, 5 days, and 30 days following surgery. Several days may pass before contact with the family is made due to families work responsibilities. Every attempt will be made to contact the family and obtain the self-reported pain sheets. However, we realize that this will not be possible for a significant number of patients. Failure to contact families postoperatively or return of the WBFPRS sheet will not be considered a violation of protocol by the team members.

(20)

http://www.wongbakerfaces.org/

b. Study duration and number of study visits required of research participants.

A total of 48 participants undergoing SILC who are eligible will be enrolled and randomized to receive either trans-incisional rectus sheath block or intra-operative rectus sheath block under direct laparoscopic visualization by the surgeon (24 participants per group). Participants will be randomly assigned to the two treatment groups with a 1:1 allocation using a computer-generated randomization schedule placed in identical, opaque sealed tamperproof envelopes. Envelopes will be consecutively numbered on the outside with a study identification number and opened in a consecutive order when a patient arrives in the operating room. We estimate the study to be completed in 2 years. Each participant will be followed for at least 30 days. The research study visit will coincide with the routine outpatient visit approximately 2 weeks following SILC as well as a follow up telephone call from a study team member at day 1, 5, and 30 after surgery. We encourage patients to schedule an in-person follow-up visit 2 weeks following operation. However, due to scheduling conflicts and other family responsibilities, these visits are sometimes outside the 2 week timeframe. We will perform the study visit in-person at the time of the scheduled postoperative visit appointment. Failure of the family to return for a postoperative clinic visit will be recorded but not considered a protocol violation by the study team.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

Surgeons will not be blinded for the study as they will be administering the anesthetic. Anesthesiologists will not be blinded as they will be providing anesthetic care during the surgery and present in the room during the surgeons' administration of the anesthetic. The patient, patient family, the PACU team, and select members of the research team will be blinded to the method of administration of anesthetic. Blinding of this group will help to prevent bias when evaluating WBFPRS values and administering analgesic medication. Blinding of this group would not have impact on the standard post-surgical care.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

Participants will receive routine care for SILC and be managed according to best practices regardless of which group they are assigned. No current therapy will be stopped.

e. Justification for inclusion of a placebo or non-treatment group.

There is no placebo or non-treatment group as the standard of care for SILC includes the administration of local analgesia prior to incision closure and administration of intravenous or oral analgesics as needed in the post-operative stages.

f. Definition of treatment failure or participant removal criteria.

Parents/guardians may elect to not continue to participate in this study at any time. Investigators may remove participants from the study at any time for protocol violation or other reasons.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

Patients will continue to receive the standard of care when the study ends or if the participant elects not to continue in the study.

5. Inclusion/Exclusion Criteria

-Inclusion: Patients aged 10-21 years old undergoing single incision laparoscopic cholecystectomy.

-Exclusion: Patients with, sickle cell disease, allergy to bupivacaine, concurrent major surgical procedure, developmental delay or neurologic diagnosis that would interfere with post-operative pain score assessment, chronic pain medication use, chronic pain disorder or complex regional pain syndrome, anesthesiologist classification of III or greater.

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

Ropivacaine is a long-acting amide local anesthetic that has been shown to cause less cardiovascular changes than other local anesthetics. It has been shown to be effective for peripheral nerve, caudal, and lumbar/thoracic epidural blocks and produces less motor blockade than bupivacaine after caudal administration. It is less lipophilic than bupivacaine and less likely

to penetrate large myelinated motor fibers, resulting in a relatively reduced motor blockade. The reduced lipophilicity is also associated with decreased potential for central nervous system toxicity and cardiotoxicity. It is metabolized extensively in the liver and excreted in urine and displays linear and dose proportional pharmacokinetics. Ropivacaine has been shown to be generally well tolerated in children aged 1 month to 15 years regardless of the route of administration. The incidence of adverse events associated with its use is low, with nausea and/or vomiting occurring most frequently (8,9).

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

Ropivacaine has been studied as a local anesthetic both for surgical anesthesia and for acute pain management. Per FDA Drug Approval Package (1), indications and usage include: epidural block for surgery including cesarean section, major nerve block, local infiltration, epidural continuous infusion or intermittent bolus, local infiltration. It has been approved for use in adults, is less toxic to the central nervous system and heart and interferes less with motor function than bupivacaine. While the safely and efficacy of ropivacaine in pediatric patients have not been established per the FDA Drug Approval Package, there exist a number of studies in the literature that have shown its efficacy and safety in this patient population. Ropivacaine is increasingly used in the place of bupivacaine for caudal anesthesia in children because of the reported lower side effects.

One report studying the pharmacokinetics after caudal block of ropivacaine (2mg/kg) in 20 children aged 1-8 years undergoing umbilical surgery showed the free plasma concentrations of the drug were well below those associated with toxic symptoms in adults and the capacity for elimination is appears to be well developed in this patient population. They concluded that ropivacaine was well tolerated and provided satisfactory post-operative pain relief (2).

A second report investigated the pharmacokinetics of caudal 0.2% ropivacaine (2mg/kg) in 30 infants aged less than 12 months. They concluded that the total and free plasma ropivacaine concentrations after caudal ropivacaine in infants were within the range of concentrations previously reported in adult and older children. No adverse events were reported (3).

A prospective randomized controlled comparison of caudal bupivacaine and ropivacaine in pediatric patients showed equal efficacy between the two in terms of onset and duration of anesthesia. Patients were aged 1-10 years and underwent elective unilateral inguinal herniotomy or urogenital surgery. The patient in the ropivacaine group received 0.25% ropivacaine at 1ml/kg for caudal block. There were no adverse effects in the two groups (4).

A prospective, observer-blinded, randomized clinical trial in children aged 3-12 years undergoing elective umbilical hernia repair evaluated pain control after ultrasound guided rectus sheath block with 0.2% ropivacaine (0.5mL/kg) compared to local anesthetic infiltration of 0.5%

ropivacaine (0.4mL/kg). They found that ultrasound guided rectus sheath block was associated with a lower pain score and decreased use of opioid and non-opioid medications post-operatively when compared to the local infiltration group (5).

We intend to use a route of administration and dose of ropivacaine that has been previously shown to be safe and effective in the pediatric population. We therefore do not anticipate any increased risk with the use of ropivacaine as it pertains to this investigation. This study is not intended to be reported to the FDA as a controlled study for a new indication for ropivacaine or for change in the labeling or in advertising for ropivacaine.

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

Please see above.

7. Study Statistics

a. Primary outcome variable.

The primary outcome is the mean post-operative pain rating based on the Wong-Baker Faces Pain Rating Scale at three hours postop or at discharge (whichever comes first).

b. Secondary outcome variables.

Operative times, the use of intravenous/oral opioid and/or non-opioid medication in the post-operative period, duration of analgesia following surgery based on time to first rescue analgesic, intra-operative hemodynamic changes, post-operative hemodynamic changes, incidence of side-effects, and complications.

c. Statistical plan including sample size justification and interim data analysis.

This is a prospective, double-blinded, randomized controlled study comparing the efficacy of trans-incisional rectus sheath block to intra-operative, intra-abdominal rectus sheath block under direct laparoscopic visualization after gallbladder removal for providing post-operative analgesia following SILC in children. The primary outcome variable is the mean WB pain rating at 3 hours postop or at discharge (whichever comes first) based on the Wong-Baker Faces Pain Rating Scale in the post-operative period following SILC.

The sample size for this study was estimated based on the historical pain scores of patients undergoing SILC at JHACH. Historically, the mean pain score for patients undergoing SILC repair using the FLACC pain scale is 4.40 with a standard deviation of 1.78. We estimate a decrease in mean pain score to 2.9 (decrease pain score <3 is considered a clinically important goal)) for patients undergoing laparoscopic guided RSB. A sample size of 24 patients per group (total of 48) will achieve a power of 0.8 at a nominal two-sided alpha of 0.05 to detect a 1.5 decrease in pain scores between the groups. We anticipate a loss to follow up of 1%, which will have minimal impact on our sample.

Analysis of the primary outcome will be performed using a t-test or Mann-Whitney U test depending on the distribution of mean pain scores. The secondary objectives will be analyzed using a t-test or Mann-Whitney U test and Chi-square or Fisher's exact test as appropriate. We will also evaluate the change in pain scores over time. Other demographic and clinical characteristics of study participants in the two groups will be compared using a t-test, Mann-Whitney test, Chi-square or Fisher's exact test as appropriate. We will first analyze the subgroups before and after the change in inclusion criteria separately and if necessary combine the p-values using a combination test. We will also perform a pooled analysis of the combined sample. All statistical analysis will be two-sided and a p-value < 0.05 will be considered statistically significant. Statistical analyses will be performed using SAS v 9.4.

Interim analysis will be performed after enrollment of 50% in each study arm.

d. Early stopping rules.

During the interim analysis, if the difference between the mean pain scores for the groups is large enough to attain statistical significance with a p-value < 0.001, then the trial will be stopped for benefit and patients will be offered the more efficacious treatment

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

Some of the overall risks of laparoscopic cholecystectomy include bile duct injury, bile leaks, bleeding and bowel injury (21). In a study combining data from seven large studies with a total of 8856 laparoscopic cholecystectomies, serious complications occurred in 2.6% (22). A combined review of eight large studies reported the following types and frequencies of complications: bleeding (0.11-1.97%), abscess (0.14-0.3%), bile leak (0.3-0.9%), biliary injury (0.26-0.6 %), and bowel injury (0.14-0.35%) (23). The rate of wound infections and surgical site infections is lower with a laparoscopic approach than with an open approach (24). Significant bleeding from the liver bed is fairly common and found in up to 10-15% of patients (25).

Potential complications of the rectus sheath block include infection, intravascular injection, and bowel puncture. The literature has reported a very low complication rate for RSB. The Pediatric Regional Anesthesia Network (PRAN) was formed to obtain highly audited data on practice patterns and complications in regional anesthetic techniques in pediatric patients. It is a centralized database, at a number of participating centers, and includes a total of 14,917 regional blocks performed on 13,725 patients over a 3 year period. They concluded that regional anesthesia in children as commonly performed in the United States has a very low rate of complications. There were no adverse events reported for the 294 rectus sheath blocks performed (1).

Ropivacaine is a long acting amide local anesthetic and has been shown to cause less cardiovascular changes than other local anesthetics (8). It is less lipophilic than bupivacaine and less likely to penetrate large myelinated motor fibers, resulting in a relatively reduced motor

blockade. The reduced lipophilicity is also associated with decreased potential for central nervous system toxicity and cardiotoxicity (8,9). Ropivacaine has been shown to be generally well tolerated in children aged 1 month to 15 years regardless of the route of administration. Incidence of adverse events associated with its use is low, with nausea and/or vomiting occurring most frequently (9). One of the general risks of local anesthetics is local anesthetic systemic toxicity (LAST). Symptoms of LAST include altered mental status (agitation, confusion, seizures, drowsiness, coma, apnea, metallic taste, cicumoral numbness, diplopia, tinnitus, dizziness) and/or cardiovascular signs (hypertension, tachycardia, arrhythmias, hypotension, conduction block, bradycardia, asystole, Torsades de Pointes). According to pooled data of 3000 patients in 60 studies, the incidence of probable accidental intravenous injection of ropivacaine was 0.2%. Only one patient experienced convulsions and no patient showed symptoms of cardiotoxicity (9).

The overall risks of participating in the study are low. Participants will continue to receive care according to established guidelines for management of SILC.

b. Steps taken to minimize the risks.

Steps taken to minimize risk include best practices associated with the current standard of care for surgical management of SILC as well as standard of care for the administration of regional and local anesthetics.

c. Plan for reporting unanticipated problems or study deviations.

Unanticipated problems or study deviations will be reported/communicated promptly to the principle investigator as well as the appropriate body as dictated by the Johns Hopkins All Children's Hospital Institutional Review Board and Policy 103.6b. This includes submitting Form R.F.3 "Event report summary sheet" when appropriate.

Data and safety monitoring will be performed by the investigators and qualified research staff. The Johns Hopkins All Children's Hospital nursing staff and pediatric surgery team (attending physician, physician assistants, surgical fellows, surgical residents, nurse practitioners) all participate in a patient's care. This includes close observation and monitoring of patients. The primary investigator of the study will perform the monitoring data, safety, and complications.

Frequency of monitoring will be in accordance to the current standard and practice/hospital policy for patients undergoing SILC. All patients receive routine pre-operative, intra-operative, and post-operative care. Post-operative care includes the standard 2 week outpatient clinic follow up after surgery. Patients enrolled in the study will also receive a telephone call from the research investigators on days 1, 5, and 30 following surgery. The in person clinic visit and the phone call at days 1, 5, and 30 following surgery are an attempt to quantify complications following the operation. Since the information obtained at these visits is not related to our primary outcome, failure to contact the family or failure of the family to schedule a postoperative visit will be recorded but not considered a protocol violation by the study team.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

The risk associated with the release of information of this study is minimal as the information to be collected is not considered sensitive. In addition, the information to be collected is no

different than the information that is already included in the patient's medical record, aside from the WBFPRS sheet patient/patient guardians will fill out after discharge.

In accordance with HIPAA guidelines, the identity of subjects will be strictly protected. All information will be kept in a locked file cabinet and any electronic version will be kept in a password protected worksheet. All results will be reported in aggregate with patient identifiers removed.

e. Financial risks to the participants.

There is no financial risk to the participants in this study.

9. Benefits

a. Description of the probable benefits for the participant and for society.

Participants of the study may benefit from experiencing superior or improved post-operative analgesia. This could decrease or possibly eliminate the need for post-operative opioid narcotics in this group. If one method/mode of anesthetic administration is found to be superior to the other, this may change the standard practice for administration of analgesia for patients undergoing SILC repair in the future. Providing improved post-operative analgesia, with the possible elimination for need for post-operative opioid narcotics would be a benefit for future patients undergoing SILC.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

There will be no compensation for participants in this study. There will be no financial penalties for not completing this protocol, for choosing not to participate in the study, or for withdrawing from the study.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

The cost of the procedure and hospitalization will be the responsibility of the parent/guardian or insurance provider.

References

1. Polaner DM, Taenzer AH, Walker BJ, Bosenberg A, Krane EJ, Suresh S, Wolf C, Martin LD. Pediatric regional anesthesia network (PRAN): A multi-institutional study of the use and incidence of complications of pediatric regional anesthesia. Anesth Analg 2012;115(6):1353-64.

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