ROPIVACAINE WITH CLONIDINE FOR PEDIATRIC RECTUS SHEATH BLOCKS- THE MAGIC COMBINATION? - A double blinded prospective study

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A. ABSTRACT

Appendectomy is one of the most frequently performed emergency surgeries in children. Although the laparoscopic technique is minimally invasive and has become a popular approach for performing appendectomies, it is still associated with a significant amount of pain and anxiety in children. To improve analgesia and decrease postoperative anxiety in children undergoing laparoscopic appendectomies, we plan to develop a multimodal approach for pain control that includes peripheral nerve blocks, a regional analgesia technique.

Selecting the ideal nerve block for laparoscopic appendectomies is a difficult task; nerve blocks traditionally contain only local anesthetic, and it is challenging to find a local anesthetic that not only possesses minimal side effects, but also outlasts pain, relieves anxiety and improves satisfaction with pain control. For instance, even though single injection ultrasound guided rectus sheath blocks provide satisfactory postoperative analgesia after pediatric laparoscopic appendectomy, they tend to be short-lived. To overcome the limitations inherent to local anesthetics, adjuvant medications have been added to nerve blocks, with the hope that the resulting combination will provide patients with better pain control. Clonidine— an alpha 2 adrenoreceptor agonist—is one such medication, and a few small pediatric studies have shown a weak trend in favor of clonidine prolonging analgesia for some blocks, without examining its anxiolytic properties. Our preliminary experience supports the notion the clonidine may assist with pain control, as we have found that a ropivacaine/ clonidine rectus sheath blockade increases the duration of sensory blockade and analgesia. The goal of this pilot study is to build upon these observations and examine whether ropivacaine/clonidine is effective at prolonging analgesia beyond the effects of ropivacaine alone for laparoscopic appendectomies. Additionally, we plan to investigate the underlying mechanism (i.e. anxiety reduction) that may make this combination better suited for postoperative pain control. Ultimately, results from our study will help us devise better therapeutic regimens for our patients.

One hundred pediatric patients (10-17 years old) scheduled for laparoscopic appendectomy will be randomized into one of two treatment groups—the Ropivacaine Group or the Ropivacaine/Clonidine group—after which they will receive bilateral injections of the corresponding blocking agents in the posterior rectus sheath, at the umbilicus location. Patients in the Ropivacaine Group will receive ropivacaine 0.5% (20 ml), while patients in the Ropivacaine/ Clonidine Group, will receive ropivacaine 0.5% (20 ml) and clonidine (2mcg/kg).

The overall hypothesis is that the ropivacaine combined with clonidine administered via single injection ultrasound guided bilateral rectus sheath blocks is a more complete and feasible pain control approach than ropivacaine alone. We will test this hypothesis by pursuing the following specific aims: 1) determine if the ropivacaine/clonidine combination is superior in providing long-lasting analgesia to ropivacaine alone; and 2) advance the understanding of ropivacaine/clonidine rectus sheath blockade, and determine if this combination significantly improves satisfaction with pain control due to psychological benefits of clonidine.

We view this innovative study as a first step in developing an evidence-based therapeutic pain regimen for laparoscopic appendectomy. Every hour of effective analgesia counts, as it improves quality of care and reduces health care costs. Upon successful completion of this project, we will seek further support to prospectively validate this combination for other trunk blocks as well as various surgical procedures. The safety of ropivacaine/clonidine blockade should be evaluated in large scale prospective studies.

B. SPECIFIC AIMS AND METHODS TO BE EMPLOYED

Laparoscopic appendectomy is a popular and minimally invasive technique is used for removing the appendix, but it is associated with significant pain and anxiety in pediatric populations. The goal of this pilot study is to examine whether ropivacaine/clonidine is effective at prolonging analgesia beyond the effects of ropivacaine alone and to investigate the underlying mechanism (i.e. anxiety reduction) that may make this combination better suited for postoperative pain control, so that better therapeutic regimens can be offered to our patients. The overall hypothesis is that the ropivacaine /clonidine rectus sheath blockade is a more complete and feasible pain control approach after laparoscopic appendectomy. This hypothesis will be tested by the following specific aims:

Aim 1. To determine if the ropivacaine/clonidine combination can prolong analgesia, we will determine if ropivacaine/clonidine rectus sheath blockade is superior in providing long-lasting analgesia compared to ropivacaine alone. Aim 1A will compare duration of paresthesia at the umbilicus instrument site. Aim 1B will compare duration of analgesia at the same location.

The methodology will be the following:

Aim 1A: On the day of surgery, patients will be asked about paresthesia and loss of sensation around the umbilicus. We will document the time when normal sensation returns following the administration of the block. The time elapsed (in minutes) between rectus sheath blockade and the point at which normal sensation returns will be compared between the groups.

Aim 1B: Every 2 hours, we will question the patients regarding their need for pain medication and obtain their Numeric Rating Scale (NRS) pain scores for umbilicus incisional pain. We will document when the patient needs pain medication. The time elapsed (in minutes) from the rectus sheath blockade until the first request for umbilicus pain medication, as well as NRS pain scores will be compared between groups.

Hypothesis:

We hypothesize that rectus sheath injections with the ropivacaine/clonidine combination will be superior in providing long lasting analgesia compared to ropivacaine alone, increasing the duration of sensory block and analgesia, and lowering pain scores at the umbilicus incision.

Aim 2. We will determine if any improvements we observe in pain control satisfaction with the ropivacaine/clonidine combination can be attributed to clonidine's ability to reduce anxiety. Aim 2A will compare between the two groups patient, parent, and nurse NRS satisfaction scores and correlate them with post-op scores on the state-anxiety component of the State-Trait Anxiety Inventory for Children (STAIC S – Anxiety). Aim 2B will compare postoperative

STAIC S – Anxiety scores between the two groups. Aim 2C will compare within the two groups the difference between the pre and post- op STAIC S Anxiety scores to show if ropivacaine/clonidine is more effective at reducing anxiety.

The methodology will be the following:

Aim 2A: NRS pain control satisfaction scores from patient, parent and nurse will be collected at the completion of the study. State-Trait Anxiety Inventory for Children (STAIC S – Anxiety) questionnaires will be administered to both groups before surgery, and at hour 6 after rectus sheath injections. Post-op anxiety scores in each group will be correlated with satisfaction scores.Aim 2B: The postoperative STAIC S – Anxiety scores will be compared between the 2 groups. Aim 2C: The pre-op STAIC S Anxiety scores will be compared with post- op STAIC S Anxiety within each group.

Hypothesis:

We hypothesize that patients, parents and nurses will experience more pain control satisfaction with the ropivacaine/clonidine combination than with the ropivacaine alone, not only because the combination will provide longer lasting analgesia, but also because clonidine's power to reduce anxiety will lead to a concomitant decrease in pain.

C. BACKGROUND

Appendectomy is one of the most common emergency surgeries performed in children, especially in adolescents and teens. (1) At present, the laparoscopic technique has become a popular approach for performing appendectomies, (1)as it is minimally invasive and has been shown to improve patients' outcomes. (2). Despite these advantages, children often experience significant pain (3) and anxiety during these laparoscopic procedures that extends after the day of surgery, particularly those who are particularly anxious before surgery. Indeed, children who are highly anxious prior to surgery tend to have more postoperative pain, delayed hospital discharge, higher incidence of emergence delirium, sleep disturbances, and other maladaptive behavior changes that can last up to a few weeks following surgery. (4), (5)

Effective postoperative analgesia after laparoscopic appendectomy is necessary for optimal recovery. (3) By simultaneously improving analgesia and reducing side-effects from opioid use, a multimodal approach that includes peripheral nerve blocks—a form of regional analgesia—could form the crux of an effective pain control regimen for patients undergoing laparoscopic appendectomy. Despite the promise of such an approach, finding a nerve block that is suitable for patients undergoing laparoscopic appendectomies is challenging. Nerve blocks typically consist of local anesthetic alone, and it is difficult to find a local anesthetic with both minimal side effects and ability to combat pain and anxiety for extended periods of time. For instance, even though single injection nerve blocks (such as rectus sheath blocks) in combination with multimodal analgesia for laparoscopic appendectomy are helpful and minimally invasive, they do not last over the course of the most painful part of postoperative period, the first 24 hours. (6) By contrast, continuous peripheral nerve blocks can provide enduring analgesia, but they are costly and deemed excessively invasive in the context of this minimally invasive surgery.

To overcome the challenge of developing a blocking agent that has both minimal side effects and duration long enough to outlast the pain, additional substances (epinephrine,

clonidine, dexamethasone, tramadol, buprenorphine, midazolam, dexmedetomidine, and ketamine) have been added to the local anesthetics comprising the nerve blocks. (7) (8) Among the adjuvants, clonidine—an alpha 2 adrenoreceptor agonist—has been shown to prolong the duration of analgesia when administered in the epidural space in children. (9), (10) Clonidine has also been added to local anesthetic for peripheral nerve blocks, but its perineural use is controversial and its exact mechanism of action is unclear; from the limited available data, perineurally administered clonidine appears to be safe, with an efficacy that has yet to be determined. Meta-analyses conducted in adult populations have found that clonidine from 30-300 mcg prolongs the time to the first analgesic request by only 2-2.5 hrs. (11) (12)

The pediatric literature regarding the use of clonidine for peripheral nerve blocks lags behind adult literature and is conflicting. Few small and under-powered studies showed at best a weak trend in favor of clonidine. (13), (14) (15) (16), (17), (18), (19) A retrospective review of 215 patients showed that the use of clonidine in conjunction with local anesthetic is effective in some locations but not others, prolonging analgesia in infraclavicular, lumbar plexus, femoral, fascia iliaca and sciatic nerve blocks by 20-50%. The increased duration of sensory blockade, however, was also associated with an increased the incidence of motor block. (16) No pediatric or adult studies were performed involving trunk blocks such as rectus sheath, transversus abdominis plane, or paravertebral nerve blocks. Side effects reported after neuroaxially or peripherally administered clonidine in conjunction with local anesthetic are hypotension, sedation, fainting, and prolonged motor blockade. (12) (16), (11) (13) Clonidine 1-2 mcg/kg is suggested for use with local anesthetic for single injections peripheral nerve blocks. (20)

Minimal sedation can be desired for some pediatric patients that underwent surgeries. Clonidine produces effective sedation for patients on mechanical ventilation that can be uncomfortable because anxiety, pain and endotracheal intubation. (21) Clonidine at 2 mcg/kg prevents sevoflurane-induced agitation (22), (23) and can be used as premedication in children. (24), (25) Oral clonidine can relieve postoperative anxiety, and subsequently improve pain control. (26) No studies have investigated its role as an anxiolytic when added to local anesthetic for a nerve block.

Preliminary studies:

The Children's Hospital of Pittsburgh of University of Pittsburgh Medical Center (CHP of UPMC) has a dedicated service that performs peripheral nerve blocks on a regular basis. Over the last academic year, 190 patients (10-17 years old, 126 patients) that underwent laparoscopic appendectomy had peripheral nerve blocks (rectus sheath and transversus abdominis plane). Our experience suggests that children localized the majority of their pain to the umbilicus instrument site. (6) To treat this pain is crucial, as this pain interferes with eating, bedside activities and ambulation, and can delay discharge.

Our preliminary study (retrospective chart of 50 patients that underwent laparoscopic appendectomy) demonstrates that rectus sheath blocks, which target pain at the umbilicus instrument, are as effective as a combination of transversus abdominis plane and rectus sheath blocks, which target pain at all instrument sites. This is an important finding, as it means that instead of dividing the amount of local anesthetic delivered between four sites,

more anesthetic can be delivered bilaterally to a single location. This can result in analgesia that lasts around 12 hours, which is relatively short for our purposes but still an improvement.

Dr Visoiu's prospective study demonstrates that postoperative pain scores after laparoscopic appendectomies correlate very well with postoperative anxiety (Pearson coefficient =0.539;133 subjects, 11-17 years old). Patients that received regional anesthesia for laparoscopic surgeries reported less anxiety after surgery (Spearman coefficient = -0.143, p = 0.042; pending publication; 202 subjects, 11-17 years old). The use of single injection nerve blocks predicts less postoperative pain (p=0.04), better mood (p=0.009), less catastrophizing thoughts about pain (p=0.007).

Based on our experience and preliminary studies, our goal is to treat the patient comprehensively, rather than just the pain itself; whenever possible, we should seek to decrease postoperative anxiety and improve satisfaction with pain control. Recently, we added clonidine to ropivacaine for rectus sheath blockade and noticed longer lasting paresthesia and analgesia (18-22 hours). Because we did not investigate the anxiolytic properties of clonidine, we do not know if the small increase in analgesia we observed is clinically relevant. The potential benefits for patients, families, and medical providers need to be investigated.

Laparoscopic appendectomy is associated with significant pain and anxiety in pediatric populations. The goal of our study is thus to investigate whether the combination of ropivacaine and clonidine is effective in prolonging analgesia beyond the duration observed with ropivacaine alone for pediatric patients undergoing these procedures. Additionally, we will explore the underlying mechanism that may make this combination better equipped for postoperative pain control, so that we can devise more optimal pain control regimens. Our hypothesis is that ropivacaine/clonidine is a significantly better therapeutic regimen for our patients. The primary aim is to determine if the ropivacaine/clonidine combination is superior in providing long-lasting analgesia. The secondary aim is to determine if the ropivacaine/clonidine combination significantly improves satisfaction with pain control due to the psychological benefits of clonidine.

D. RESEARCH DESIGNS AND METHODS

Overview

This is a double blinded prospective study. Following University of Pittsburgh IRB approval, 100 pediatric patients will be recruited. Following parental written consent and patient assent, these patients will be included in the study.

Patient eligibility

Inclusion criteria will consist of 1) age 10-17 years, 2) scheduled for elective laparoscopic appendectomy, 3) weight >/=34kg, 4) complete postoperative questionnaires. Exclusion criteria will be 1) patients younger than 10 years and 18 years or older, 2) weight < 34 kg, 3) weight >/=100 kg, 4) patient and family refusal, 5) non-English-speaking patients and families, 6) cognitive impairment, 7) developmental delay, 8) allergies to medications used in the study (hydromorphone, oxycodone, acetaminophen, ketorolac, ropivacaine, and clonidine), 9) need for opioids via a patient controlled analgesia device, 10) patients with a positive pregnancy test, and 11) local infection at planned injection sites

The following patients will be excluded from the study: 1) patients with failed rectus sheath blocks, 2) patients that require opioids via a patient controlled analgesia device, 3) patients with laparoscopic procedure converted to open, 4) patients that will not be able to place the time of return to normal sensation within 1 hour of its occurrence (e.g. sleeping), and 5) patients with no follow-up possible. The patients that will be discharged home before the resolution of paresthesia will be excluded from analysis of the first aim.

Randomization:

The operating room pharmacy will perform the randomization using a computer-generated random number table. The study medications will be labeled as study drug and released in identical syringes with a volume of 11 ml each. Two syringes will be released per patient. Each syringe for Ropivacaine Group (total 2) will contain 10 ml of ropivacaine 0.5% and 1ml of normal saline. Each syringe for the Ropivacaine/ Clonidine Group (total 2) will contain 10 ml of ropivacaine 0.5 %, 1 mcg/kg (0.01 ml/kg) of clonidine (100 mcg =1 ml) and normal saline for a total volume of 11 ml. Patients and all members of the care team, except the pharmacist, will be blinded to group allocation.

Intraoperative Study Protocol:

In the operating room, standard anesthesia monitors will be connected and general anesthesia will be performed as per the anesthesiologist's standard of care. At the completion of surgery, acetaminophen iv and ketorolac will be administered by the anesthesia provider. Dexmedetomidine will not be administered during anesthesia or after the completion of anesthesia. A member of CHP Acute Interventional Perioperative Pain Service (AIPPS) – attending or fellow will perform all bilateral ultrasound guided rectus sheath blocks as per CHP standard of care using the study drug. The surgeon will not infiltrate the local anesthetic at the laparoscopic instrument sites.

Postoperative Study Protocol:

For the following 24 hours, the analgesic regimen will include ketorolac every 6 hours (if not contraindicated by surgeon), acetaminophen iv every 6 hours, oxycodone by mouth as needed for pain, every 4 hours, and hydromorphone iv as needed for pain, every 2 hour.

In the postoperative period the patients will be asked to complete a few questionnaires created for this study. The nurse taking care of the patient, principal investigator, one of the co-investigators, or the research assistant will do the assessment. Starting in the PACU, the patients will be questioned about the presence of paresthesia around the umbilicus instrument site ("is the area around your belly button numb") and the umbilical pain severity using NRS scale (0 being no pain and 10 the worst imaginable pain). They will also be asked about their need for pain medication for umbilical pain as well as the amount of pain medication they have consumed for pain in that region. The assessment will continue on the floor every 2 hours until complete resolution of paresthesia at the umbilicus or until the patient is discharged home. The state version (S-anxiety) of the State-Trait Anxiety Inventory for Children (STAIC) will be administered to measure patient anxiety before surgery after the consent is done and 6 hours after rectus sheath injections. At the completion of the study,

the patient's, parent's, and nurse's satisfaction with pain control will be investigated using an NRS scale (0 being very unsatisfied and 10 being very satisfied).

E. STATISTICS: ASSESSMENT OF ADEQUACY OF SAMPLE SIZE

Descriptive statistics will be presented as frequencies (percentages, %) for categorical data or as mean ± standard deviation (SD) or median and interquartile range for normally or non-normally distributed continuous data, as appropriate. Examination of normal distribution assumption for continuous data will be determined by q-q plots and histograms. Two sample T-Test or Wilcoxon-Mann-Whitney test will be performed to determine differences between groups for normally or non-normally distributed continuous data, respectively. Pearson's chi-square or Fisher's exact test, as appropriate, will be used to compare the frequency distribution of categorical variables between the groups. We will compute Pearson correlation coefficient between NRS pain scores and the anxiety scores. If the assumptions for the parametric test are not met, a nonparametric alternative will be used (i.e. Spearman correlation coefficient).

Sample Size and Power:

The target sample size was calculated with the assumption that the duration of block in the group with ropivacaine only is 720 minutes ± 288 minutes and in the group with ropivacaine and clonidine the duration is 1080 minutes ± 432 minutes. The difference would be clinically relevant if the duration of blocks with ropivacaine and clonidine will be at least 50% or more than the duration of blocks with local anesthetic only. Assuming a power of 80%, a level of significance of 0.05, mean and SD as above, only 12 patients would be required in each group. Allowing for a 400% loss arising from patient dropout, unsuccessful block, incomplete follow up because of discharge home on the day of surgery, and inability to determine when paresthesia wears off, we plan to recruit 50 patients in each group, for a total of 100 patients. We estimate that this sample size of 100 patients would provide 80% power to detect a difference as small as 23% in the duration of paresthesia between these 2 groups.

F. SIGNIFICANCE AND APPLICABILITY

To our knowledge, this is the first study to investigate if ropivacaine /clonidine rectus sheath blockade is a better and more complete therapeutic regimen for patients undergoing laparoscopic appendectomy. While the patients that underwent uncomplicated laparoscopic appendectomy are treated as inpatients for at least one day, CHP wants to implement early discharge strategies. Unfortunately, the pain after the day of surgery can be significant (3), and causes some parents to be reluctant to have their children discharged. Analgesia advice can be poorly retained (27) and parents can feel overwhelmed about home pain management. Furthermore, some parents believe that using pain medication in childhood may lead to later drug abuse. (28) This is particularly concerning, as parents often undermedicate their child's pain, with up to 60% of parents administering less than the prescribed analgesia on the following day after surgery discharge. (29), (30) A child with long lasting pain control and less anxiety from ropivacaine/clonidine rectus sheath blockade would help the parent better cope with the surgical event, facilitating early discharge.

We would like to mention that patient's satisfaction with pain control is becoming an increasingly important aspect of health care reimbursements reported via the Hospital Assessment of Healthcare Providers and Systems (HCAHPS) survey. The ropivacaine/ clonidine rectus sheath blockade in combination with multimodal therapy can serve as a better therapeutic regimen than the standard of care, improving quality of care, increasing satisfaction and saving health care costs.

G. POTENTIAL LIMITATIONS AND FUTHER DEVELOPMENT

First, although we will record the pain scores and analgesics consumption for pain located at the umbilicus instrument size, our data is subject to some bias. These predictors of analgesia may be prone to misclassification. The visceral/gas pain can be confused with incisional pain, and some patients will need analgesics for another type of pain and location. We believe that using paresthesia as surrogate for analgesia is a better and more complete indicator of duration of analgesia.

Second, preoperative anxiety may reflect in postoperative anxiety scores. However, we believe that comparing preoperative and postoperative anxiety and pain scores will help minimize this bias.

Third, other medical researchers maybe interested in the ropivacaine/clonidine effectiveness on trunk blocks (paravertebral, transversus abdominis plane blocks, ilioinguinal) for other surgical procedures. Upon successful completion of this project, we will seek further support to prospectively validate this combination for other trunk blocks as well as various surgical procedures. Finally, we acknowledge that to assess the safety, the participation of a substantially larger numbers of centers is required.

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STUDY DURATION:

The study period is from the time of the consent until postoperative block resolution assessment is completed and estimated to be 18-24 hours for each patient.

TIMELINE: The proposal will not extend 2 years.

VERTEBRATE ANIMALS: Not applicable for this project

INSTITUTIONAL APPROVAL: IRB will be needed