1. **Title of Project:**
   Awake caudal catheter infusion versus general anesthesia and single-dose caudal injection for preterm NICU patients undergoing inguinal herniorrhaphy.

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3. **Abstract:**
   This is a prospective, blinded, randomized controlled trial evaluating the effectiveness of awake caudal catheter infusion versus single dose caudal injection and general anesthesia in the surgical management of preterm infant inguinal hernia repair. Currently, the standard of care in the United States is general anesthesia. Spinal anesthesia has been advocated for but highly rejected in the pediatric surgical community due to its high failure rate which can be up to 28%. Spinal anesthesia is a form of regional anesthesia involving injection of a local anesthetic into the subarachnoid space, via a fine needle, in a single injection. The failure rate has to do with the time constraint of spinal anesthesia which is approximately 1 hour. It is difficult to perform a bilateral inguinal hernia in that time duration, necessitating a return trip to the operating room for the contralateral side or intubation midway through the surgical case. We hypothesize that awake caudal catheter infusion will allow for the following benefits (1) greater than 2 hour anesthetic time via redosing which will allow for the completion of the planned surgical procedure (2) exhibit a negligible failure rate (3) minimize post-operative complications that have been associated with general anesthesia in the preterm neonate.

4. **Background:**
   It is well established that preterm inguinal hernias discovered in the NICU pose a significant surgical risk due to the associated co-morbid conditions that accompany these patients. There have been studies that have established that elective outpatient repair of inguinal hernias found in the NICU can be safely performed. However, due to the low associated risk of incarceration and subsequent bowel loss many institutions are reluctant to treat this way and practice is widely variable (Sulkowski JP, 2015). The most common practice in NICUs across the country is to wait until the patient is ready for discharge from the NICU and to perform inguinal hernia repair prior to discharge (Crankson SJ, 2015). This allows for the patient to undergo significant growth in the NICU without increasing the risk of incarceration. Currently and historically this operation is performed under general anesthesia, which requires the preterm neonate to be intubated during the procedure and depending on their respiratory status, sometimes afterward. A recent review of current practices in regards to inguinal hernia repair in the United States demonstrated that 70% of repairs are performed with general anesthesia (Wiener ES, 1996). Due to the known risk of apnea and bradycardia in the preterm infant, alternatives to general anesthesia for inguinal hernia repair has been hotly debated in the surgical, anesthetic, and neonatology literature. General anesthesia with single-shot caudal injection is an established practice with demonstrated safety. A study utilized this technique where 91 out of 126 patients safely underwent general anesthesia and caudal injection (Murphy, 2008). Recent studies suggest that low gestational and postconceptional age, low birth weight, anemia, and complicated past medical history affect respiratory complication rates, particularly apnea in formerly premature infants undergoing elective inguinal hernia repair (Ozdemir T, 2013). Spinal anesthesia is currently the most common anesthetic procedure used in the surgical treatment of preterm inguinal hernias after general anesthesia, although spinal anesthesia is not currently in wide surgical practice due to its high failure rate that is up to 28% in some studies (López T, 2012). Spinal anesthesia in the preterm infant has been found to decrease apneic events as well as decrease post-operative prolonged mechanical ventilation, although the latter is disputed in the literature (G, 2003)

(Craven PD, 2003). A significant portion of this failure is due to the short duration of anesthetic time, which is less than 1 hour depending upon patient weight. Therefore, it is hard to make a surgical argument for its preferential use. An alternative to spinal anesthesia that results in an ability to sustain regional anesthetic effect for a longer duration is the caudal catheter infusion. Caudal anesthesia is hailed as the single most important regional anesthesia technique in children (M, 2015). Compared with neuraxial techniques in adults, it can be easily learned and reproduced (Schuepfer G, 2000). The caudal catheter technique has been previously reported in multiple publications and textbooks to safely provide post-operative neuraxial analgesia in pre-term/low-weight/neonatal patients. Caudal catheter technique involves placement of a small catheter under ultrasound guidance into the caudal epidural canal to allow re-dosing of local anesthetic during the case and has been shown to be safe and effective management in neonates (Somri M, 2007). Ultrasound guidance has been demonstrated to be fundamental for the performance of successful posterior approaches in pediatric patients (Kirchmair L, 2004). Ultrasound guided placement of caudal anesthesia is also successfully used in patients with difficult anatomy (Schwartz D, 2008). The use of peri-operative analgesic blocks has also been shown to result in quicker awakening and a more comfortable postoperative course (Conroy JM, 1993). Current literature has showed caudal anesthesia with a failure rate of less than 5% which is significantly less than spinal anesthesia (Geze S, 2011) (Marhofer P, 2015) (Wong SY, 2004) (Hosseini Jahromi SA, 2012). Currently, there is only one published article that has used single-injection caudal injection in the management of preterm NICU inguinal hernias (Geze S, 2011). There were no reported adverse events and no failures in a sample of 15 neonates.

If the results of the study support the hypothesis, this contribution could be significant and impact clinical practice and the standard of care by allowing surgeons to safely perform the operation in an adequate time period. In addition, it could decrease preterm neonatal post-operative complications, which are significant. In general, pediatric surgeons are leaders in surgical innovation which has been shown in the rapid advancement of laparoscopic techniques and minimally invasive procedures. Once it is established that the completion rate with awake caudal catheter technique in preterm infant hernias is high without increasing morbidity and mortality, there should not be a significant argument against its use. It has already been established that regional anesthesia has a significant benefit to the preterm infant (Tobias JD, 1992). As a prospective, randomized trial it also is attempting to reach the gold standard in clinical research as opposed to a retrospective trial. This research project is a study that other investigators could continue to build upon for its other possible indications. Awake caudal catheter technique is useful analgesia in procedures that occur below the level of the umbilicus. In other high-risk pediatric patients, this technique has the potential to be used in lower extremity surgical procedures as well as urologic procedures (Londergan TA, 1994). Caudal catheter placement is performed by a significant number of anesthesiologists, but the reinforcement of its benefits by this paper has the potential to increase its application and awareness among the community. The neonatologists' community as well as the NICU patients would benefit from solid evidence that the use of regional anesthesia can be effectively used as an alternative to general anesthesia in some surgical instances. Therefore, our study has the ability to change clinical practice in three distinct fields of medicine.

5. Specific Aims:

An elective operative procedure on preterm neonatal patients has long been debated among pediatric surgeons, neonatologists, and anesthesiologists. Anesthesia in this particular group of patients pose a significant risk due to their associated medical conditions which can be multiple and quite varied. The most common risk factor for these neonates undergoing general anesthesia is their inherent bronchopulmonary dysplasia which ranges from mild to severe. It is well

established that general anesthesia in preterm infants can cause apnea and bradycardia (Welborn LG, 1994). Recent literature has shown the effectiveness of spinal anesthesia for preterm NICU inguinal hernias in the prevention of apnea and bradycardia immediately post-operatively (Rukewe A, 2010). Spinal anesthesia has significant drawbacks, resulting in failure to gain wide acceptance in the pediatric surgery community. Depending on the size of a pediatric patient, spinal anesthesia may not last one hour and can therefore lead to a failure rate of up to 28% (López T, 2012). That is a significant factor for pediatric surgeons who can complete a bilateral inguinal hernia repair with general anesthesia virtually 100% of the time. Caudal catheter infusion allows for greater than two hours of operating time for the pediatric surgeon without the use of general anesthesia. That would be an adequate amount of time to perform a preterm neonatal bilateral inguinal hernia.

Our long-term goal is to establish if there is a significant medical benefit to preterm infants by measuring their time to return to baseline respiratory function and by monitoring occurrences of apnea and bradycardia post-operatively after hernia repair. Our overall objective is to establish if awake caudal catheter infusion in NICU inguinal hernia repair is a safe and effective alternative to general anesthesia and single-shot caudal injection. Our central hypothesis is that NICU inguinal hernia repair can be completed with a close to 0% failure rate and that the avoidance of general anesthesia and therefore intubation in these patients will result in a faster return to baseline respiratory function and fewer instances of bradycardia and desaturations. We plan to test our central hypothesis and thereby accomplish our overall objective for this project by pursuing the following two specific aims:

1. To investigate if caudal catheter infusion in preterm infants during inguinal hernia repair has a low failure rate which allows for completion of the operation without the use of general anesthesia.
    - We hypothesize that awake caudal catheter infusion in preterm infants will result in a less than 96% failure rate.

2. To determine if a significant medical benefit can be demonstrated between the use of awake caudal catheter technique versus single-dose caudal injection and general anesthesia in regards to respiratory status, bradycardia, and apnea post-operatively.
    - We hypothesize that awake caudal catheter technique when compared with single-dose caudal injection and general anesthesia will be of greater benefit to preterm infants via the following primary quantifiable measures: reduction in the time to return of baseline respiratory function, reduction in the number of apneic episodes (defined as cessation of breathing by a premature infant that lasts for more than 20 seconds and/or is accompanied by hypoxia or bradycardia), and a reduction in bradycardic events (heart rate <90).
    - We hypothesize that secondary measures will be of greater benefit to preterm infants as well with decreased days to hospital discharge, decreased number of post-operative narcotic use days, decreased mechanical ventilation days, and decreased time to full oral feeds.

Such results are expected to advance the field of pediatric anesthesiology and pediatric surgery which will impact clinical practice by changing the peri-operative management of high risk NICU patients.

6. **Research Plan:**

Inclusion and Exclusion Criteria

Patients included in the study are preterm infants in the NICU less than 50 weeks post gestational age born at less than 37 weeks gestational age. Patients will be within 1 week of meeting NICU discharge criteria with or without supplemental oxygen prior to surgical scheduling for inguinal hernia repair. Males and females will be included in this study, but there is a known higher incidence of male inguinal hernias in the literature, approximately 6:1.

Patients undergoing other invasive procedures including but not limited to gastrostomy tube placement, tracheostomy, and/or laser eye treatments will be excluded. Any patient with a medical condition that would prevent a regional anesthetic from being performed (i.e. bleeding diathesis, vertebral anomalies, spinal cord injury prior to surgery) and any contradictions to the prescribed medications in the protocol will be excluded.

This will be a prospective, blinded, randomized controlled clinical trial. When the NICU staff and surgeon decide that inguinal hernia repair is warranted, a research representative will approach the family for research consent. Dr. Bryskin and Dr. Felema will provide the anesthesia for both groups and will obtain anesthesia consent on the day of surgery. The general anesthesia and single-shot caudal group will be induced with intravenous (IV) propofol 3mg/kg and rocuronium 0.6mg/kg and intubated. Caffeine 15mg/kg and rectal Tylenol 30mg/kg will then be given for apnea prevention and pain control. Caudal will be performed under ultrasound guidance with bupivacaine 0.25% + 1:200,000 epinephrine (total dose 2.5mg/kg) prior to start of the surgery. At the conclusion of the operation, neuromuscular blockade will be reversed with neostigmine and glycopyrrolate. The patient will be extubated once criteria are met. If the patient is unable to extubate within 20-30 minutes, they will be transferred to the NICU intubated with assisted ventilation. The general anesthesia group will not receive narcotics for pain management intra-operatively due to the increased risk of apnea and bradycardia. Since the study is attempting to answer whether the act of exposure to general anesthesia changes the likelihood of apnea and bradycardia, we need to maintain the same approach to pain management in both groups. No Precedex will be given in the general anesthesia group. Pain management in the NICU will be the following: mild to moderate pain based on a FLACC scale will receive rectal or oral Tylenol, while moderate-severe pain will receive IV morphine 0.05mg/kg.

In the caudal infusion group, Precedex 0.5 mg/kg IV will be administered for sedation over 10 minutes and maintained with an infusion of 0.7 mg/kg/h. Under ultrasound guidance a 20 gauge angio-catheter will be placed into the caudal space and secured to the skin with a tegaderm. A low volume extension catheter will be connected to the angio-catheter and bupivacaine .3% + 1: 200,000 epinephrine (dose 3mg/kg) will be administered via the catheter. An additional dose of 1mg/kg will be administered at 1 hour post initial dosing time to extend the duration of the caudal. Intravenous caffeine and rectal Tylenol will be administered for apnea prevention and additional pain control. If patient agitation is noted during the operation, an additional bolus of Precedex 0.5 mg/kg will be administered. If agitation persists, pain, and/or respiratory distress are noted during the operation, general anesthesia will be induced with propofol 3 mg/kg and rocuronium 0.6 mg/kg followed by endotracheal intubation. The angio-catheter will be removed at the end of the surgical procedure. Pain management in the NICU will be the following: mild to moderate pain based on a FLACC scale will receive rectal or oral Tylenol, while moderate-severe pain will receive IV morphine 0.05mg/kg.

Blinding of the study will occur on the day of surgery by the anesthesiologists. Prior to a patient arrival to operating room, the anesthesiologist will randomly draw an envelope from a folder that will allocate group assignment (this precludes bias while discussing patient care with parents and getting consent). It is etimated that we will need approximately 20 patients in each group. 10 evelopes at a time will be placed in the folder, 5 will be in the awake caudal catheter group and 5 will be in the general anesthesia and single-dose caudal group. This will keep the numbers equal when going forward with the study.
Intra-operatively, neither the anesthesiologist nor the surgeon will be blinded since they are present from the induction of anesthesia until the conclusion of the operation for patient safety. The pre-operative, intra-operative, and post-operative care by the NICU will be blinded. All patients will have had a caudal procedure (single vs. catheter) and extubation will be attempted in all patients prior to NICU transport. If extubation cannot be accomplished within 30 minutes following completion of the operation, the patient will be transported to the NICU intubated. Since post-operatively the same medical personnel cannot be used in every case, a protocol sheet will be placed at patient's bedside as a reference material. This is also a way to provide continuing education about the study and who should be contacted if there is a concern that escalation in narcotics use is indicated.

Blinding of the NICU staff will be maintained since in an extubated patient, there will be no way to determine allocation based on the caudal wounds. In the intubated patient it will not be clear whether the patient started out intubated or was intubated because of a caudal failure. Since the intra-operative anesthesia approach will be standardized, there will be no additional information that the NICU staff will require. The anesthesia record will be placed in a sealed envelope in the chart prior to departure from the OR. The NICU staff will be able to unseal the envelope in the event that rescue patient management is needed or if it is felt to influence management. In addition, personal contact information for the two anesthesiologists involved in the study will be provided to the staff in the event there would be an urgent question requiring clarification. The envelope label will also instruct medical records personnel to open the envelope and make contents part of the patient's medic record upon hospital discharge. A letter will be sent to parents upon discharge specifying their child's group assignment.

A research specialist and two other surgeons will have completed CITI courses and be available to give informed consent to parents for the study. Baptist IRB will be submitted for approval after acceptance by the CRRC. Cases are normally scheduled 3-7 days ahead of time so the research specialist should have sufficient time to perform the consent process. In the event that the research specialist is unavailable, another trained surgeon will be accessible. Although we will try to prevent selection bias in the NICU, there is bound to be times when parents will opt out of the randomization process and will elect to have either general anesthesia and single-shot caudal or caudal catheter infusion. Those patients will still be consented for use of their data in the study. At the time of manuscript preparation, those patients will be identified as refusing randomization.

Inguinal hernia repair will be performed by one of five pediatric surgeons employed by Nemours Children's Clinic in the same standard fashion. Key components of the operation include groin incision and a high ligation of the hernia sac, which is the standard of care in the United States. Laparoscopic inguinal hernia repair will not be performed in these patients for three reasons: Firstly, so that there is standardization among surgeons performing the operation and secondly for statistical analysis. Thirdly, there is only one surgeon that performs this operation routinely. Caudal catheter placement and infusion will be performed and monitored by Dr. Bryskin and Dr. Felema who are employed by Nemours Children's Clinic in the Department of Pediatric

Anesthesiology. Having a limited number of anesthesiologists performing the standardized intra-operative approach will also allow for excellent quality control of the study.

Statistical Analysis

Currently, there are no published articles in the literature to help generate a level of data which can be used to determine the power analysis. We would want a power of 80% and a significance level of 0.05 for the study and after the first 10 patients are enrolled we can calculate a reliable sample size. Based on previous studies conducted in a prospective, randomized fashion we approximate approximately 20 patients in each arm though this is only speculation until the first ten patients are enrolled (Oghazian MB, 2015) (Rakhshani A, 2015) (Mathur NB, 2015). A review from 1/1/2014 – 12/31/14 of NICU patients undergoing inguinal hernia repair at Wolfson was performed and totaled 21. We estimate approximately 80% study inclusion and 20% exclusion. Jobayer Hossain, a Nemours statistician will perform all statistical analysis of the study and has indicated the following will be used in the analysis. Demographic and baseline data will be summarized by treatment groups, namely general anesthesia and caudal catheter groups. Quantitative variables will be summarized by mean/SE or median/interquartile range (IQ), whichever appropriate. Categorical variables will be summarized by frequencies and percentages. A chi-square or Fisher exact analysis will be used to compare the general anesthesia group and the caudal catheter infusion group in the primary outcome, which is time to return to baseline respiratory function. A Cox hazard model ratio will compare the hazard risk between the two groups and a log rank test will calculate the median time to return to baseline function. In addition, a Cox proportional hazards model will be used to compare the risk of failure between two groups. A poisson regression analysis will compare the number of bradycardic events, apneic events, catheter complications, and number of post-operative narcotic use days between the general anesthesia group and the caudal catheter infusion group. A logistic regression model will be used to compare the proportion of successful surgical completion between two groups. We estimate the study will run two years for adequate patient accrual. Data will be input by the research nurse and sent for analysis to the statistician for periodic review every three months. Primary outcomes that will be analyzed in the statistical analysis are: time to return of baseline respiratory function, successful surgical completion, catheter complications, number of apneic episodes (defined as cessation of breathing by a premature infant that lasts for more than 20 seconds and/or is accompanied by hypoxia or bradycardia), and bradycardic events (heart rate <90). Secondary outcomes are: days to hospital discharge, number of post-operative narcotic use days, operative time, mechanical ventilation days, and time to full oral feeds.

7. **Possible Discomforts and Risks:**

Adverse events associated with caudal catheter placement or single-shot caudal placement are very low. This procedure is routinely done in neonatal surgery. The most common complications are infection which in a large study is less than .03% and failure of adequate pain control which is less than 5%.

If, for some reason, the catheters do not work, your child will be intubated and general anesthesia will be given. The patients in the general anesthesia and single-dose caudal injection will only receive an injection after they are intubated and not placement of a catheter.

8. **Possible Benefits:**

We believe that this technique for pain management in preterm infants will improve post-operative complications that are common to the NICU which include decreased respiratory rate and low heart rate.

9. Conflict of Interest

No conflict of interest exists with the PI or investigators.