Identification of the optimal analgesic dose of intrathecal hydromorphone for pediatric patients undergoing posterior spine surgery for idiopathic scoliosis

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Title:

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Specific Aims:

Intrathecal opioid administration is a widely used and effective analgesic strategy for a variety of patient populations and surgical types.[1-14] Intrathecal opioids can effectively produce analgesia, but can have variable spread, duration, effectiveness, and side effects based on the pharmacodynamics and pharmacokinetics of the opioid used as well as differences in individual patient metabolism and physiology. Furthermore, prior literature suggests that the dose of intrathecal opioid is procedure specific, with thoracic, abdominal, and spine procedures requiring higher doses than less invasive surgeries.[9] Thus, it can be difficult to determine a single "optimal dose" due to alterations to each of these variables for any given procedure.

Intrathecal opioids have proved useful in providing analgesia for surgical patients. Specifically, Intrathecal morphine (ITM) use at a variety of doses has been widely reported as an analgesic technique used in pediatric spine surgeries.[1,3,6,7,11,15-18] In contrast, intrathecal hydromorphone (ITH) use, which may be associated with a lesser frequency of side effects, has not been reported. Our clinical experience shows the need to identify a dose of ITH that balances analgesic efficacy with the risk for toxicity in our pediatric idiopathic scoliosis repair population. Opioid equivalencies can approximate an ITH dose based on ITM doses, but a wide range of ITM doses has been reported.[1-3,6-8,16-18] Additionally, this approach does not account for any differences in drug metabolism or challenges in interpreting and applying opioid equianalgesic tables.[19]

Ultimately, we would like to provide a dose of ITH that provides adequate analgesia but minimizes side effects such as respiratory depression, excessive sedation, unanticipated escalation in level of care, and prolonged recovery room or hospitalization times. To accomplish this goal, the Specific Aim of this study is to perform a dose finding study in our adolescent patients undergoing idiopathic scoliosis repair to identify the ED90 dose for ITH.[20] The evidence-based identification of an optimal (ED90) weight-based analgesic ITH dose in this population that avoids severe opioid induced side effects has substantial positive safety, financial, and patient satisfaction implications.

Background and Significance:

Many analgesic methods have been utilized for pediatric spine surgery, but the optimal methods are still debated. The use of ITM at a variety of "low" and "high" dose ranges has been well described, with early studies showing a dose dependent analgesic benefit for 18-48 hours.[1,2] A 2019 meta-analysis conducted by Musa et. al examined the addition of ITM for postoperative pain management in pediatric spine surgery.[7] They examined a total of 5 studies including 3 randomized controlled trials and 2 retrospective chart reviews identifying 636 pediatric patients. The doses of ITM described in this meta-analysis ranged from 2 mcg/kg to higher than 20 mcg/kg.

More recently, intrathecal hydromorphone (ITH) administration has been added to the analgesic regimen used at our institution for patients undergoing idiopathic scoliosis repair. This transition was made in part due to temporary national shortages of Preservative-Free morphine, but also in response to side effects experienced with ITM. Our clinical impression is that ITH provides adequate analgesia for 18-24 hours, often eliminating the need for supplemental IV or PO opioid administration during that time. However, some patients have been quite sedated in recovery, requiring prolonged post-operative care unit (PACU) stays, rapid response team activation for hypopnea with desaturation, unexpected elevations in the required level of care, or naloxone administration beyond what is stipulated in the protocol for pruritis.

The current perianesthetic protocol for idiopathic scoliosis patients undergoing idiopathic scoliosis repair includes an anxiolytic premedication, postoperative nausea and vomiting prophylaxis, total intravenous anesthetics until neuromonitoring is completed, ITH, and a multimodal analgesic regimen. One variable that remains inconsistent among different anesthesiologists is the mcg/kg dose of ITH that is administered. In a review preparatory to research, the median dose is 4.42 mcg/kg (IQR 3.8-4.9 mcg/kg), with a range that includes a four-fold variation in dose (1.6 to 6.9 mcg/kg). In the literature, generally a 2:1 conversion ratio of morphine: hydromorphone is accepted.[10,12,21] However, there are very broad ITM doses reported in the literature, ranging from 2 mcg/kg to 40 mcg/kg and as much as 1 mg.[3,6,7,13,16] For pediatric spine surgery specifically, doses reported range from 2 mcg/kg to more than 20 mcg/kg.[7] Furthermore, the definitions of "low dose" and "high dose" are different depending on the study; in one study, "high" doses of 5 mcg/kg were shown to result in decreased blood loss without improved analgesic benefit over 2 mcg/kg for pediatric spine patients.[16] Thus, the currently accepted range of ITM doses reported in the literature, even amongst pediatric spine patients, is broad, and there is considerable variability in the ITH doses in our clinical practice.

Although both hydromorphone and morphine are hydrophilic opioids that spread rostrally when administered in the neuraxis, morphine produces a greater rostral spread.[9] Further, accurate conversion between opioids in the intrathecal space may not be captured by existing equivalency tables. Potency, or the dose required to achieve a certain drug effect, can differ wildly among opioids and individuals, and interacts differently with therapeutic windows and toxicity thresholds.[19,22] ITM has been well documented to have a ceiling effect, at which analgesic benefit is maximized and side effects begin to become problematic.[9] This is likely true for ITH as well, but the doses have not been defined.

Studies have also shown differences in potency and analgesic effect depending on the type of pain and which pain fibers are activated in addition to which specific opioid is chosen.[22-24] Sviggum et al defined the ED90 doses of ITM (150 mcg) and ITH (75 mcg) for primary cesarian section for an adult obstetric population using a sequential allocation biased-coin method.[20] As a follow up study, Sharpe et al compared ITH and ITM in the same population. They used a 2:1 morphine:hydromorphone ratio and did not find any statistically significant differences in analgesic outcomes or side effect profiles between the ED90 doses of ITH and ITM.[12,20] This is the only study in the literature directly comparing these two opioids administered intrathecally at an evidenced-based ED90 dose, and used much lower doses than we are currently using for pediatric spine analgesia (75 mcg of ITH, which is 3-4 fold less than the current median dose [depending on patient size]). Compared to the large amount of literature available on ITM (despite the wide range of doses proposed for pediatric patients), this study would be novel in that the examined opioid is ITH in a specific pediatric surgical population. We would also be able to clarify on the wide range of intrathecal opioid dosing that is currently reported for pediatric spine surgery. Therefore, results would be directly translatable to our practice and others that may favor ITH over ITM for pediatric spine patients, minimizing side effects while maximizing analgesia.

Proposed Research Methods:

Regulatory approvals

Institutional IRB approval will be sought under a drug protocol (pending IRB submission). Registration at clinicaltrials.gov will take place prior to patient enrollment. Written informed consent will be provided by parents. Assent will be provided by patients (written vs. verbal depending on age).

Setting

Recruited patients will have surgery in Nassf Tower at St. Mary's Hospital. They will recover in the Nassf Tower PACU and remain inpatient at St. Mary's following surgery.

Participants

Targeted number: 40 patients

Inclusion criteria: ASA 1-2 patients aged ≥10-17 years undergoing spinal surgery with a posterior approach for idiopathic scoliosis.

Exclusion criteria: Patients with pre-surgical elevated pain scores (≥3/10 on Numeric Rating Scale (NRS)), history of chronic pain, or pre-surgical opioid use will not be included. Patients with contraindications to spinal anesthesia (anatomical abnormality or elevated bleeding or infection risks) will not be included. Patients for whom the protocol is violated (inability to perform postoperative data collection), or the study/procedure was aborted will not be included in analysis.

Recruitment procedures

Subject recruitment will be performed by the study coordinator and/or one of the study investigators during 1) the pre-operative listing appointment with orthopedic surgery or 2) the pre-operative anesthetic evaluation in the PACU of Nassf Tower on the morning of surgery. Attempts will be made to provide families with study material for their review in advance of their arrival to the hospital on the day of surgery. If necessary, communication via a pre-operative phone call, video visit, and/or portal message may take place to relay study information prior to surgery.

Procedure

Randomization

No randomization will take place for this study.

Study Intervention

This sequential coin based up-down dose allocation method is based upon the prior work of Sviggum et al and Durham et al, with the goal of identifying the ED90 for ITH in idiopathic adolescent scoliosis repair via the posterior approach.[20,25,26] A starting dose of 3.5 mcg/kg of hydromorphone was determined by current practice at our institution as well as upon review of available literature of previously used ITM doses in pediatric spine patients.[7,13,18] This dose is somewhat less than the median dose in current clinical practice (4.4 mcg/kg). Subsequent participants will receive higher (step "up") or lower (step "down") from this starting dose. Steps "down" from the starting dose will be smaller than steps "up" to ensure maintenance of adequate analgesia and to allow more accurate estimate of the optimal dose should it decrease beyond our starting dose. Steps "up" from the starting dose were chosen based on commonly used weight-based doses in our current practice. A maximum dose of 400 mcg, despite patient weight, was determined based on expert consensus and review preparatory to research query. The possible doses (mcg/kg) for ITH will be as follows (starting dose underlined):

2 – 2.25 – 2.5 – 2.75 – 3 – 3.25 – <u>3.5</u> – 4 – 4.5 – 5 – 5.5 – 6 – 6.5 - 7

ITH will be provided by a care team member not involved in patient consent or data collection. The anesthesiologist covering the case (high lumbar or thoracic corrections) or the surgeon (low lumbar corrections) will administer the medication at the low lumbar level. Patients and outcome assessors will be blinded to doses administered. Postoperative course will be followed by an inpatient pediatric pain service with independent authority for managing and ordering analgesic medications for at least 24 hours after intrathecal drug administration. The managing providers on this service will be blinded to the dose of ITH.

ITH dose adjustments for subsequent study patients will be based on the efficacy of the dose used with the prior patient. Efficacious ITH administration will be defined as all NRS scores ≤5 within the first 18 hours after administration (binary outcome). Doses for subsequent patients will be adjusted using a biased coin up–down sequential allocation method described by Durham and Flournoy[25] with the aim of estimating the ED90 for ITH. When ED90 is to be determined ($\tau = 0.9$), the probability (B) = $(1 - \tau)/\tau = (1 - 0.9)/0.9 = 0.1/0.9 \approx 0.11$. If the NRS score was >5 within 18 hours or if the patient required supplemental opioid administration for pain control (suggestive of insufficient analgesia), the dose will be increased for the next enrolled study patient. If the pain score remains ≤5 within 18 hours of opioid administration, the next patient will receive with probability $B \approx 0.11$ the next lower dose and with probability $1 - B = 0.89$, the same dose as the previous patient. Patients excluded after randomization will be removed from the study. The next recruited patient's dose assignment will be adjusted based on the same biased-coin sequential allocation process as if the excluded patient had not been enrolled.

Other Aspects of Care

Patients will receive standard of care as our current spine protocol outlines for idiopathic adolescent scoliosis repair. This includes a ketamine/midazolam/acetaminophen oral premedication that allows for awake IV placement, IV induction of anesthesia, and initial maintenance of anesthesia on remifentanil

and propofol infusions to allow for neuromonitoring. Patients will be provided postoperative nausea and vomiting (PONV) prophylaxis with ondansetron, dexamethasone, and scopolamine. 0.25 mcg/kg/min of intravenous naloxone for pruritis will be initiated prior to extubation. Patients will be extubated following the surgical procedure in the operating room and will recover in the postoperative anesthesia care unit. In the first 24 hours after intrathecal opioid administration, patients will have multimodal analgesic options available. Unless contraindicated, they will receive liposomal bupivacaine at the incision site, and IV ketorolac and PO acetaminophen will be scheduled postoperatively. IV fentanyl and PO oxycodone will be available as needed for moderate to severe pain scores.

Assessments

Postoperative pain assessments will be conducted by the PACU nurses, floor nurses, and APRN via the pediatric pain service for at least 24 hours and until pediatric pain consultation is no longer required by the surgical service, or until the time of hospital discharge.

- *Primary outcome:* Pain intensity will be reported by the patient using an 11-point numeric visual analogue scale (NRS) with 0=no pain and 10=worst pain ever.[27] Efficacious ITH administration will be defined as all NRS scores ≤5 within the first 18 hours after administration (binary outcome).
- *Secondary outcomes:* We will identify the incidence of need for dual anti-pruritic agents (Nubain or naloxone (beyond the protocol infusion rate of 0.25 mcg/kg/min)), maximum pain scores and OME consumption during the first 24 hours after intrathecal administration, and incidence of antiemetic use postoperatively as a marker for PONV. Pain intensity will be collected at regular intervals during the first 24 hours after intrathecal opioid administration with a goal of at least 4 NRS pain score collections in this time period.
- *Adverse events:* Adverse events potentially related to ITH will be defined as respiratory depression or excessive sedation identified via RASS scores ≤-3 in the first 24 hours postoperatively, requirement for unanticipated PCU/ICU level care rather than the general care floor, or additional naloxone (beyond protocol infusion rate) at any time within 24 postoperative hours. If any of these events are encountered and deemed to be possibly related to the ITH dose after review by the consensus of 3 independent pediatric anesthesiologists, then the next enrolled study patient will receive the next lower dose allocation. These pediatric anesthesiologists (names TBD) will not be involved in the patient's perioperative care and will be blinded as to ITH dose. Case demographics and pertinent history will be provided to these individuals and they will determine based on this review if they think that the ITH could have contributed to side effects.

Statistical analysis

No formal statistical sample size analysis will be performed. Simulation studies have suggested that using 20 to 40 patients in up–down sequential allocation trials will provide stable estimates of the target dose for most realistic scenarios. In addition, the nonindependence and unknown distribution of data of an up–down study prevent the development of theoretically rigorous rules to calculate the necessary sample size.[28] We will use the algorithm as described above (Study Intervention) and in Durham and Flournoy[25] to determine dose allocations during the recruitment process. Briefly, this will involve sequential dose adjustments based on the presence or absence of acceptable analgesia as well

as the presence or absence of intolerable side effects. Confidence intervals for ED90 will be determined using methods as described in Sviggum et al.[20]

Isotonic regression using the pooled adjacent-violators algorithm will be used to determine the modified isotonic estimator for the ED90 dose.[20] In short, the observed success rate (percentage of patients with NRS pain ≤5 for 18 h) will be calculated for each dose. Isotonic regression using the pooled-adjacent-violators algorithm will then be used to obtain point estimates for the success rates that were constrained to be monotonic increasing with dose. The modified isotonic estimator for ED90 will then be obtained via linear interpolation between the highest dose with an estimated success rate <90% and the lowest dose with an estimated success rate >90%. To provide an interval estimate for ED90, and for the probability of success at the sample estimate for the ED90, a 95% confidence interval (CI) will then be constructed using the bootstrap approach described by Stylianou et al.[21] Supplemental analyses of secondary endpoints for each study medication will be restricted to doses that were used for at least 10 study patients. In all cases, 2-tailed tests were performed with P values <0.05 will be considered statistically significant.

Anticipated results and limitations

With completion of this study, we expect to identify a dose at which patients experience adequate analgesia without significant dose-limiting side effects.

Limitations include a multitude of pain scoring methods used in pediatric patients, varied pain score collection practices among different care providers, and possibility of poor coping and pain catastrophizing in this unique patient population which could artificially skew results.[29] In addition, these patients are expected to progress through routine anesthesia care, PACU care, and postoperative floor care; areas which all have different practices regarding assessment and treatment of pain in children and adolescents. Another limitation is the subjective nature of assessing adverse events, should they occur. Our existing spine protocol is detailed and includes several other medications which could contribute to sedation in the postoperative period. It may be difficult to delineate side effects due to intrathecal opioid alone versus a multifactorial issue.

Risks

The current standard of care for many pediatric spine surgery centers includes intrathecal opioid administration. Risks inherent to this study design do not differ from risks encountered in daily clinical practice and include risks related to the procedure itself (bleeding, infection, spinal headache), as well as potential side effects related to opioid exposure. These include but are not limited to urinary retention, ileus, constipation, sedation, respiratory depression, and pruritis.

Next steps

Knowing the ED90 dose of ITH will allow us to adequately treat adolescent idiopathic scoliosis patients with an evidence-based dose while avoiding the side effects we have been seeing in recovery and on the floor. Additional pediatric patient populations are receiving intrathecal opioid with regularity in Nassf Tower, including patients undergoing anterior approach scoliosis repair and Nuss procedures. In the future, ED90 doses could be identified for different surgical populations to allow for more precise analgesic dosing.

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Rules for ITH STUDY Patient Management – Posterior Spine Repair for Idiopathic Scoliosis

Laminated copy to accompany patient during transfer from OR→PACU→floor

Questions? Please contact study PI: [redacted]

INTRAOPERATIVE CARE

Follow standard preexisting spine protocol (remifentanil/propofol infusions, PO premedication, antiemetic regimen, etc). Note any deviations to protocol.

Naloxone gtt to be started in OR prior to extubation at a rate of 0.25 mcg/kg/min

Anesthesiologist administering (or giving dose to surgeon for administration) ITH is the only person to know the dose.

Pain assessors (nurses, pain service) must be blinded to dose.

POSTOPERATIVE ANALGESIA:

Patient will be followed by the Inpatient Pediatric Pain Service [redacted] at least 24 hours following intrathecal opioid administration. Questions/concerns regarding pain management should be directed to this service.

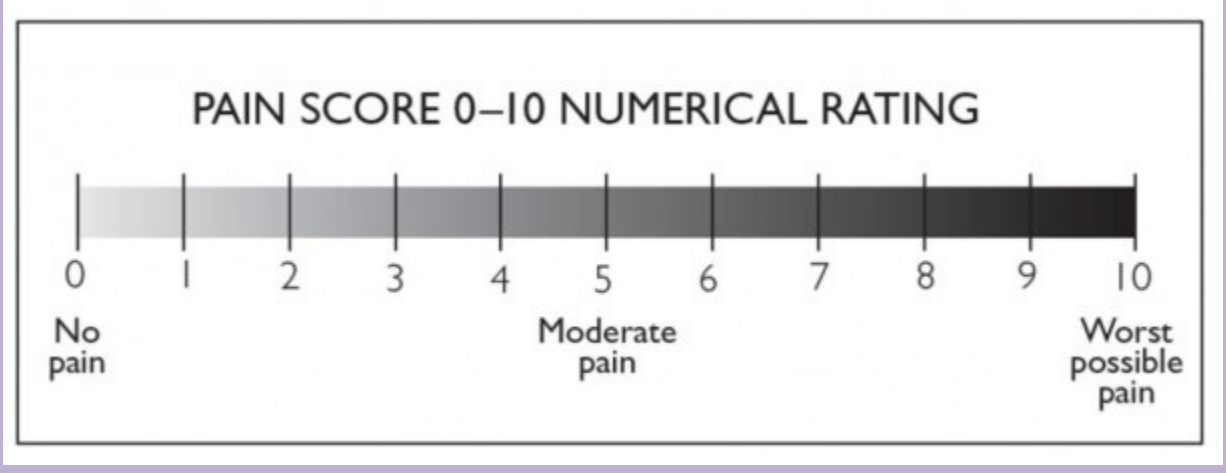
Unless contraindicated, patients should receive liposomal bupivacaine at the incision site. IV ketorolac and PO acetaminophen will be scheduled postoperatively. IV fentanyl and PO oxycodone will be available as needed for moderate to severe pain scores.

PAIN ASSESSMENTS:

Patients need pain assessments in PACU and on floor.

Must use Numeric Rating Scale to assess pain.

Goal is at least 4 documented NRS scores within the first 18-24 hours post-ITH administration.



NRS=Numeric Rating Scale
ITH=Intrathecal hydromorphone