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**Title** Pain outcomes in children who received intrathecal versus intravenous opioids for pain control following major urologic surgery: A retrospective review.

**Running head:** Intrathecal vs. intravenous opioids in children undergoing urologic surgery

**Article category:** Original research

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**What is already known:** Intrathecal opioid administration has been associated with short term postoperative benefits including reduced pain and opioid use and longer interval to morphine rescue in children.

**What this study adds:** Intrathecal opioids were associated with reduced need for intravenous opioids for the first 16 hr after urologic surgery with no discernible difference thereafter. Children who received intrathecal opioids experienced higher rates of pruritus, constipation and hypotension than those who received intravenous opioids.

**Implications for translation:** Intrathecal opioids are a suitable analgesic alternative to intravenous opioids in children undergoing major urologic surgery. Given that the analgesic benefits of intrathecal

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opioids are short-lived, it is important to transition the children to oral or IV analgesics in a timely manner to avoid unrelieved pain.

## **Abstract**

*Background:* Intrathecal (IT) opioid administration has been associated with postoperative benefits including reduced pain and opioid use in children. However, the postoperative benefits and risks of IT opioid administration during major urologic surgery in children remain unclear.

*Aim:* To compare postoperative pain and adverse event outcomes among children who received IT vs. intravenous (IV) opioids during major urologic surgery.

*Methods:* We reviewed the medical records of children 3-17 years of age who underwent ureteroneocystostomy or pyeloplasty between 2006 and 2012. Electronically captured anesthetic and surgical data, PACU and nursing flowsheets, and daily progress notes through hospital discharge were reviewed. Analgesic techniques (i.e.: IT or IV patient/nurse controlled opioids), all analgesic drugs and doses were recorded. Outcome measures included pain scores, need for rescue analgesics, opioid-related adverse events and their treatments.

*Results:* 77 children received IT opioids and 51 received IV opioids. More children in the IV group required rescue analgesics and had higher pain scores at PACU discharge. Children in the IV group required rescue opioids more frequently than the IT group from 0-8 hr. and 8-16 hr. after PACU discharge, but rates were similar by 16-24 hr. 70% of children in IT group transitioned directly to oral opioids. 7 IT placements were considered as failed due to early need for rescue opioids. 4 (8%) of the IV group and 7 (9%) of the IT group experienced oxygen desaturation. 2 of these, both in IT group required naloxone and 1 was admitted to ICU for observation. The IT group experienced a higher incidence of pruritus, constipation and hypotension.

*Conclusion:* We observed better post-operative pain control in children who received IT vs. IV opioids for the first 16 hr. with no discernible difference thereafter. The intrathecal group experienced higher incidences of pruritus, constipation and hypotension.

**Key Words** (6): Postoperative analgesia, intrathecal opioids, urologic surgery, children.

## **Introduction**

Intrathecal (IT) morphine has been used as an analgesic adjuvant during cardiac, orthopedic, abdominal and urological surgery in children (1, 2). Several randomized trials have shown that children who received IT morphine intra-operatively had reduced pain and opioid requirements in the post-operative period following hypospadias repair (3), cardiac surgery (4) and spinal fusion(5). In this latter study, children had also received intravenous (IV) opioids via the patient controlled analgesia (PCA) method. Retrospective studies, in children who underwent a variety of surgeries, similarly found those who received IT morphine in addition to general anesthesia had reduced intraoperative and postoperative opioid use compared to those who received nalbuphine PCA (5-7) Studies have also found that in

children who received IT opioids the interval to IV morphine rescue was longer compared to those who received intra-operative IV opioids alone (3, 4, 8) or IT placebo (2, 6, 9). A retrospective review of 187 children receiving low dose IT opioids for a range of major open and laparoscopic surgical procedures found that 16% of patients did not require any post-operative opioids (7).

Although the short-term postoperative benefits of IT opioid administration during surgery have been demonstrated, little is known about related adverse events. Retrospective data vary showing that pruritus, nausea and vomiting are the most common side effects across a range of IT opioid doses with an incidence of these effects varying from 6% (3) to 35% (7). Urinary retention rates for children who received IT opioids has also varied widely, from 3% (7) to 59% (6, 10, 11) More serious adverse effects of IT opioids include sedation and respiratory depression(9, 12) and post dural puncture headache (1, 7, 8). However, randomized controlled trials comparing IT and IV opioids have found similar and low rates (< 5%) of respiratory complications in both groups (3, 4).

Larger, multi-center registries of anesthesiologist self-reported pediatric regional cases have, to date, included only a small proportion of cases where IT block was used ( $\leq 2\%$ ), and these have reported few major adverse events (10-12). In one of these, a single case of inadvertent intravascular injection (of unspecified intrathecal medication) was reported among 506 IT injections (10), and in another, three of 386 cases had "extended spinal blocks/total spinal anesthesia" (11). From the Pediatric Regional Anesthesia Network (PRAN) database which included cases from North America, only one adverse event (i.e., hypotension in an adolescent girl) was reported in 83 IT blocks (12). Although these databases suggest a very low rate of serious complications from IT injections, they do not differentiate between IT anesthesia and IT analgesia, nor give details of the drugs used. Significant adverse events are reported but rates of common side effects are not. From these self-reported registries, use of IT opioids, bupivacaine, or combined drugs could not be discerned, and thus, there are sparse data regarding outcomes related to IT analgesia.

Despite these studies, the benefits and risks of intraoperative IT morphine as they pertain to the postoperative course following major urologic surgery in children remains unclear. We, therefore, designed this study to retrospectively review and compare pain and adverse event outcomes among children who received IT vs. IV opioids for postoperative pain management following major urologic surgery.

#### **Methods:**

Approval was obtained from the Institutional Review Board at the University of Michigan Medical School, and a waiver of consent was granted to collect de-identifiable patient data for this study. We used our anesthesia electronic database (Centricity; General Electric Healthcare, Waukesha, WI, USA), to identify all children 3-17 years of age who underwent ureteroneocystostomy or pyeloplasty. During 2009 and 2010, the use of regional anesthesia had expanded at our institution and, specifically, IT administration of morphine became a routine practice to manage pain for children having major urologic

surgery. Prior to this time, analgesia was managed using IV delivery of opioids either by patient controlled analgesia (PCA) pump or nurse controlled administration (NCA). For this study, we included children who underwent surgery between 2006 and 2012, to ensure a sufficient sample who had received either IT or IV opioid delivery over a period during which the surgical practices remained largely unchanged. We excluded children who received non-IT regional analgesia (i.e., epidural or caudal blocks), and children under three years of age (to reduce the potential for unreliable self-reported pain scores).

Trained research assistants carefully reviewed the medical records of all subjects and recorded the following data: patient demographics, ASA physical status, surgical procedure, anesthetic technique, and routes and amounts of all intra- and postoperative opioids and adjuvant analgesics administered. Duration of induction (i.e., time from onset to incision), surgery (i.e., incision to surgical dressing time), emergence (i.e., surgical dressing completed to extubation) and hospital stay were calculated from electronically captured data.

The following outcome data were also recorded from the post-anesthesia care recovery unit (PACU) and nursing flow-sheets for each 8 hour period after PACU discharge for 24 hours, and during each 24 hour period thereafter until hospital discharge: highest pain scores (i.e. 0-10 numeric pain ratings), depth of sedation (i.e. University of Michigan Sedation Scores 0-4, where 0=awake/alert to 4=unroutable) and vital signs including lowest SpO<sub>2</sub> from continuous pulse oximetry capture (routine in our setting), lowest respiratory rate (RR), heart rate (HR) and systolic blood pressure (BP).

All analgesic-related and surgical adverse events and their treatments were identified from review of flow-sheets, progress notes (surgical and acute pain team), and medicine administration record through 30 days after discharge (via clinic documentation). Adverse events and their possible treatments included: pruritus (diphenhydramine), nausea/vomiting (antiemetic), oxygen desaturation and respiratory depression (naloxone and supplemental oxygen), constipation (laxatives), hypotension (defined as a 20% decrease from baseline and/or requirement of an IV fluid bolus), infection (i.e., fever with/without treatment), and post-dural puncture headache (with / without blood patch treatment). All children for whom spinal analgesia was placed or attempted were included and failed IT analgesia was defined as the need for IV opioid rescue in less than 8 hours following IT injection. The medical records of children who were identified as having a failed spinal, post-dural puncture headache, escalation of care or with any other questionable data underwent a secondary and independent review by one of the anesthesiologist investigators (i.e. EMP or PK) to ensure the integrity and reliability of data.

Statistical Analysis: All analyses were conducted with SPSS version 21 and data are presented as n (%) or mean  $\pm$  standard deviation. Comparisons for nominal data (e.g., sex) were made between groups using chi-square with Fisher's exact tests. Continuous variables were compared using unpaired t-tests (corrected as appropriate based on Levene's test for equality of variance). Opioids were converted to morphine equivalents per kilogram of the child's weight and were standardized to the time spent in the hospital, for comparisons. Pain scores were treated as continuous data, and a repeated measures

analysis of variance was used to compare pain scores between groups. Statistical significance was accepted if p values were < 0.05, and Bonferroni corrections were applied for the repeated measures.

## Results

One hundred fifty-eight children underwent ureteroneocystostomy or pyeloplasty during our study period, however, 30 children were either <3 years of age or had received an excluded regional technique. Thus, data from 128 patients were analyzed. Seventy-seven children had received IT hydromorphone (all after 2009), and 51 (96% from 2006-2008), IV opioids as their primary mode of postoperative analgesia. There were no significant differences in ASA status, gender, and age or operation type between the IT and IV groups (table 1).

### *Perioperative Data*

Table 2 presents a description of the intraoperative care of children in the groups. There was a small but significant increase in the induction time for children in the IT group. Sixty-two (81%) children in the IT group had co-administration of bupivacaine 0.75% (mean volume  $0.04 \pm 0.015$  ml/kg) and none had bupivacaine without IT opioid. Preservative free morphine (Duramorph) was the IT opioid used in all patients and the mean dose was 4.4 mcg per kg ( $\pm 0.59$ mcg). As expected, the intraoperative analgesia management of children differed significantly between the two groups (see table 2). Additionally, in the post anesthesia care unit (PACU), significantly more children in the IV group required rescue opioid (table 2).

### *Postoperative analgesia outcomes:*

After PACU discharge, children in the IV group received opioids via PCA/NCA pump (n=41 [80%]) or intermittently as needed (n=10 [20%]). In contrast, a majority in the IT group were transitioned directly to oral opioids (n=54 [70%]), while fewer received PCA/NCA (n=12 [16%]) or intermittent IV (n=9 [12%]) opioids. Nearly all children in the IV group (n=49 [96%]) required IV opioids within the first 8 hours after PACU discharge, compared to only 11 (14%) in the IT group ( $p < 0.001$ ). In seven (9%) of the IT cases, the anesthesiologist had documented difficulty with the technique and these were, thus, recognized as having failed at the time of placement. Overall, the time to the need for opioid rescue in the IT group was  $15.6 \pm 7.9$  hours (Median 19; range 0-33; IQR 13-21 hours).

The proportion of children who received opioids was also greater in the IV group from 8-16 hours postoperatively (47 [92%] vs. 25 [33%];  $p < 0.001$ ) but was similar by 16-24 hours (46 [90%] vs. 70 [91%];  $p = 0.892$ ). Total opioid use over the course of the hospital stay was significantly higher for the IV group compared to the IT group ( $0.01 \pm 0.005$  vs.  $0.005 \pm 0.004$  mg oral morphine equivalents/kg/hour of stay;  $p < 0.001$ ). Conversely, acetaminophen use was higher for the IT group ( $1.48 \pm 1.04$  vs.  $0.72 \pm 0.67$  mg/kg/hr of stay;  $p < 0.001$ ) and ketorolac administration was not different ( $0.01 \pm 0.02$  vs.  $0.01 \pm 0.02$  mg/kg/hr;  $p = 0.154$ ). As shown in the figure, average pain scores for both groups were, overall, low and there was a large and significant effect of time from baseline (PACU), where scores went up for the IT group, but did not change for the IV group (Interaction Time\*Group tested with Wilks' Lambda 2.76;

p=0.032; partial eta squared 0.324). There was no main effect for group (IV/IT) on pain scores in this sample (F 0.498; p=0.484; partial eta squared 0.011).

*Adverse events:*

The overall incidence of opioid related adverse effects was higher for the IT group (75% vs. 67%), however this did not reach statistical significance in this sample (p=0.092) (Table 3). The incidence of bothersome but not dangerous side effects, including nausea, vomiting and pruritus, was high in both groups. The rates of pruritus, constipation and hypotension were significantly higher in the IT group. The rates of respiratory compromise were similar in both groups and included: 7 cases of oxygen desaturation in the IT group (9%)—5 requiring supplemental oxygen, and 4 (8%) in the IV group, all requiring oxygen. Of these, two children (both in the IT group) required naloxone administration in the PACU and one was admitted to the intensive care unit for observation. Due to the clinical presentation of these patients, an inadvertent opioid overdose was suspected and documented. There was no difference in the length of hospital stay between the two groups (IT group  $2.48 \pm 1.59$  days; IV group  $2.74 \pm 0.41$  days; p = 0.413).

During the 30-day follow up period, two children in the IT group and four in the IV group had complained of nausea and vomiting just following discharge from hospital. Similar numbers in both groups reported ongoing pain: 7 (9%) in the IT group and 5 (10%) in the IV group. Two children in the IT group had reported headache without intervention in the early days after discharge. The documented details of headache in these cases were inconsistent with diagnosis of post-dural puncture headache.

**Conclusion:**

Similar to previous studies in children, our study shows a reduction in intra- and postoperative opioid use in patients who received IT opioids compared to IV only opioids (2-4, 13, 14). A small majority of children (53%) who received IT opioids did not require an opioid rescue until  $\geq 18$  hours after surgery, and more than two-thirds transitioned directly to oral analgesics without the need for IV opioids. Pain scores were low for children in both groups and did not significantly differ. These findings suggest that IT opioid analgesia provides benefit in terms of reduced analgesic need in the early post-operative period only; we found that 16 hours after PACU discharge both IT and IV opioid administration were similarly efficacious in managing postoperative pain.

Our finding that IT administration of opioids reduced postoperative opioid requirements during the early postoperative period is consistent with those from other studies (4, 8). The length of time-to-rescue in our study is consistent with other studies, ranging from 12.3 to 22.9 hours depending on the dose of IT morphine (3, 15). Such data regarding the expected time to need for analgesic rescue may facilitate effective transition to oral or IV opioid or adjuvant analgesics and thereby avoid severe unrelieved pain. As seen in figure 1, we found a consistent albeit modest increase in pain intensity in our IT group at the time we expected the IT analgesia to become ineffective. Early supplementation with non-opioid agents during the early postoperative period in our study, may have resulted in only modest increase in pain scores once IT analgesia wore off with elimination of opioid need altogether in some patients.

The relatively high incidence of bothersome but non-serious adverse effects in our sample is higher than has been previously reported. Our incidence of nausea and vomiting was roughly double that found in studies (7, 8) where more than 100 children were followed-up for 48 hours. Lower rates of nausea and vomiting (between 6 and 8%) may reflect very short follow-up times (3) or less major surgical procedures (2). The high incidence of pruritus in our IT group is similar to that reported in other studies (7). Lower rates of pruritus (e.g. 10%) have been found for children treated prophylactically with naloxone infusion (6) and in those not followed beyond the early postoperative period (2). Interestingly, we found a higher rate of constipation in the IT group vs. the IV group, a comparison that has not been made in previous studies. Our incidence of respiratory depression is similar to other studies with incidence varying from 1 – 10% across a range of follow-up periods. Two children in our sample required naloxone. While an overdose was suspected, these children may have been highly sensitive to opioids. This highlights the need for safety measures for children receiving opioids via any route. These should include postoperative monitoring (e.g., pulse oximetry), careful drug preparation, delivery, and “time-outs.”

Despite somewhat equivocal findings regarding benefits and risks in our study, administering morphine intrathecally may offer some advantages over other routes of opioid administration. Firstly, the procedure itself has a clear end point (free flow of CSF) compared with other regional methods, such as epidural administration. In our study we found a high success rate for IT analgesia (i.e., 86%), similar to other studies (7) and the majority of failures had been identified at the time of attempted IT injection. Secondly, IT administration requires smaller opioid doses than intravenous or alternative regional routes, as it enables direct access to central and spinal cord opiate receptors (16). Overall, children in our IT group received lower doses of opioids both intra-operatively and post operatively. In theory, lower overall opioid doses should be associated with fewer side effects; however, this was not the case. In our study and others, similar adverse effects were found when opioids are given via IT and IV routes. Thus, the opioid-sparing effect of IT opioids has, to date, not been associated with a decrease in opioid-related adverse effects and a much larger sample may be needed to demonstrate this effect. Finally, there may be a cost benefit related to the rapid transition to oral analgesia and reduced need for IV medications or PCA pump equipment during the hospital stay.

The retrospective nature of this study introduces several potential biases that may limit the interpretation of our data. Firstly, data were collected over the period where the IT technique was first introduced which may have inflated our failure rate. Additionally, our pain and adverse event outcomes were based solely on medical record documentation which introduces a significant potential of reporting bias. However, given that documentation of these outcomes is mandatory by institutional standards and captured electronically, our concern for this bias is lessened. Our study also has strengths that have not been noted previously. These include a rigorous exclusion and inclusion criteria which has not been used in previous retrospective studies. Further, we limited our sample to a large group of children operated on by the same urologic surgeons over a small time period. Generalizing our findings beyond this setting may be difficult given potential differences in surgical, anesthetic, and postoperative practices. However,

similar findings in our study as in previous studies, lend external validity to our findings.

In summary, the intraoperative administration of IT opioids in our sample was associated with better postoperative analgesic efficacy than IV opioids alone during PACU stay and for the first 16 hours after PACU discharge. Additionally, intraoperative administration of IT opioid was associated with a delayed need and/or no need for intravenous opioid rescue analgesics for a majority of children. We found higher rates of the opioid-related adverse outcomes of pruritus, constipation and hypotension in the IT group. These data can be used to inform perioperative and postoperative analgesic management for children undergoing major urologic surgery with an aim to improve safe and effective use of opioids.

#### **Disclosures:**

This work received a waiver from the Institutional Review Board of the University of Michigan Medical School on February 12, 2012; IRB # HUM00055997.

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Conflicts of interest: No conflicts of interest are declared.

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Table 1: Characteristics of the Study Groups (data presented as n (%) or mean  $\pm$  SD where applicable)

	<b>Intrathecal (n=77)</b>	<b>Intravenous (n=51)</b>	<b>P Value</b>
Age (years)	7.24 ± 3.40	8.0 ± 2.97	0.232
Female	57 (74.0%)	30 (59%)	0.071
ASA 1	20 (26.0%)	17 (33.3%)	0.194
2	56 (72.7%)	31 (60.8%)	-
3	1 (1.3%)	3 (5.9%)	-
Pyeloplasty	18 (23.4%)	16 (31.4%)	0.36
Ureteroneocystostomy	59 (76.6%)	35 (68.6%)	-

Table 2. Description of Perioperative Data (presented as n (%) or mean ± SD)

	<b>Intrathecal (n=77)</b>	<b>Intravenous (n=51)</b>	<b>P value</b>
Anesthesia induction (minutes from start to end)	43.6 ± 13.3	37.8 ± 16.0	0.027
Surgery duration (minutes from incision to dressing)	220.5 ± 83.9	227.1 ± 75.5	0.652
Anesthesia emergence (minutes from dressing end to extubation)	11.3 ± 11.2	13.8 ± 10.9	0.209
Preoperative acetaminophen	20 (26%)	25 (48%)	0.010
<b>Intraoperative Medications</b>			
IV opioid administered	29 (38%)	51 (100%)	<0.001
IT bupivacaine	62	NA	-
Oral morphine equivalents (mean ± SD mg/kg)	0.05 ± 0.09	0.19 ± 0.10	<0.001
Ketorolac	8 (10%)	22 (42%)	<0.001
Local infiltration	17 (22%)	11 (21%)	0.901
<b>Post-anesthesia care medications</b>			
Opioids	14 (18%)	37 (71%)	<0.001
Ketorolac	6 (8%)	5 (10%)	0.716
Oral morphine equivalents (mean ± SD mg/kg)	0.01 ± 0.03	0.04 ± 0.04	<0.001
Acetaminophen	7 (9%)	3 (6%)	0.489
PACU length of stay (minutes)	97.2 ± 41.6	102.7 ± 43.2	0.474

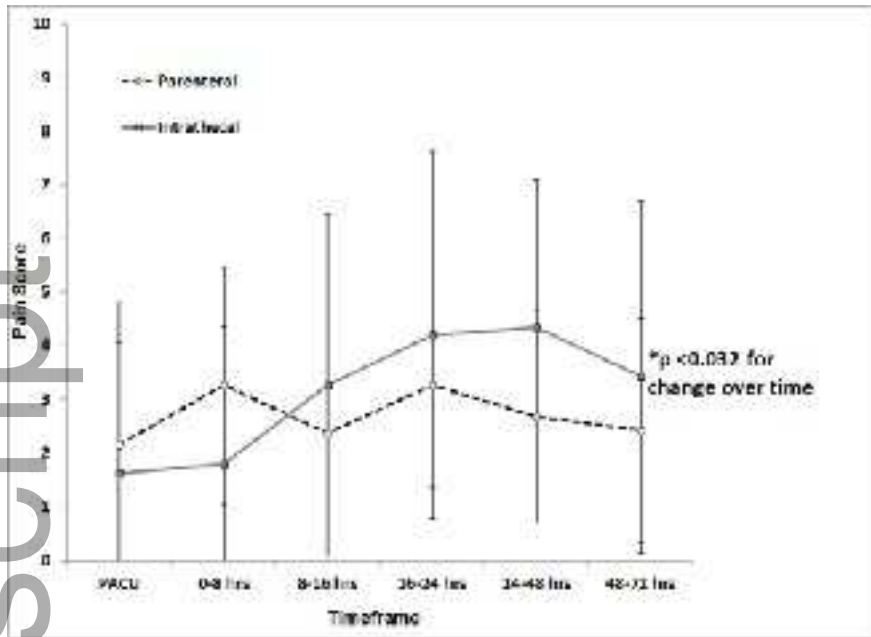
PACU=Post Anesthesia Care Unit

Table 3: Description of Adverse events (n (%))

	<b>Intrathecal (n=77)</b>	<b>Intravenous (n=51)</b>	<b>P value</b>
Overall analgesic-related adverse events	58 (75%)	32 (67%)	0.294
Nausea +/- vomiting	51 (66%)	30 (59%)	0.395
Antiemetic	39 (51%)	25 (49%)	
Pruritus	31 (40%)	7 (14%)	0.001
Diphenhydramine	15 (20%)	7 (14%)	
Constipation requiring laxative	23 (30%)	7 (13%)	0.035
Urinary retention	4 (5%)	1 (2%)	0.647
Bladder spasm	22 (29%)	13 (26%)	0.702
Oxygen desaturation (SpO <sub>2</sub> <92%)	7 (9%)	4 (8%)	0.647
Supplemental O <sub>2</sub>	5 (7%)	5 (10%)	0.432
Over-sedation	2 (3%)	1 (2%)	1.00
Naloxone given	2 (3%)	0	0.517
Hypotension requiring fluid bolus	14 (18%)	2 (4%)	0.026
Unplanned ICU admission	1 (1.3%)	0	1.00
Post-dural headache	2 (3%)	NA	-

Legend for Figure:

Reported pain scores in the groups over time.



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