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RESEARCH REPORT

A retrospective comparison of intrathecal morphine and epidural hydromorphone for analgesia following posterior spinal fusion in adolescents with idiopathic scoliosis

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What is already known

- Postoperative analgesia following posterior spinal fusion surgery remains challenging; intrathecal morphine in conjunction with morphine patient-controlled analgesia has been used to control pain in prior studies.

What this article adds

- Patients who receive intrathecal morphine for posterior spinal fusion surgery are able to directly transition to oral opioids, ambulate sooner, have their Foley catheters removed sooner, and have a shorter length of stay than those who received epidural hydromorphone at our institution.

Keywords
adolescent; scoliosis; pain; opioids; intrathecal; epidural

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Summary

Background: Posterior spinal fusion to correct idiopathic scoliosis is associated with severe postoperative pain. Intrathecal morphine is commonly used for analgesia after adolescent posterior spinal fusion; however, anticipating and managing the increase in pain scores after resolution of analgesic effect of intrathecal morphine analgesia is challenging. In 2014, we developed a clinical protocol detailing both the administration of intrathecal morphine intraoperatively and the transition to routine, scheduled oral analgesics at 18 h postoperatively. The goal of our study was to examine the efficacy of our intrathecal morphine protocol vs epidural hydromorphone for postoperative analgesia after posterior spinal fusion.

Methods: Following IRB approval, we retrospectively identified developmentally intact children of ages 10–20 years in our electronic database with a diagnosis of idiopathic scoliosis who had undergone elective posterior spinal fusion surgery from June 2014 to April 2015. For the intrathecal morphine group, intrathecal morphine was administered in a dose of 12 $\mu g \cdot kg^{-1}$ (max 1000 μg) prior to incision. Postoperatively, all children in the intrathecal morphine group had an order to receive oral oxycodone (0.1 $mg \cdot kg^{-1}$, max 5 mg) starting at 18 h postintrathecal morphine injection. For the epidural hydromorphone group, catheters were placed by the surgeon and bolused with 5 $\mu g \cdot kg^{-1}$ hydromorphone (max 200 μg) and 1 $\mu g \cdot kg^{-1}$ fentanyl (max 50 μg), followed by a continuous infusion of 40–60 $\mu g \cdot h^{-1}$, and patient-controlled bolus doses of 5 μg with a lockout interval of 30 min. All patients in both groups had postoperative orders for acetaminophen, diazepam, and ketorolac.

Results: During the study time period, 20 patients received intrathecal morphine and were successfully matched with 20 patients who received epidural hydromorphone. All patients in the intrathecal morphine group were

transitioned to oral analgesics on the first postoperative day, without need for intravenous opioids after discharge from the postanesthesia care unit. Compared to the epidural hydromorphone group, the intrathecal morphine group reported lower pain scores in the postanesthesia care unit (difference in means −4.26 [95% CI −6.56, −1.96], $P = 0.001$) and first 8 h after surgery (difference in means −1.88 [95% CI −3.84, 0.082, $P = 0.060$) and higher pain scores on the 2nd postoperative day (difference in means 1.60 [95% CI 0.10, 3.10], $P = 0.037$). The documented time to ambulation and time of Foley catheter removal were statistically earlier in the intrathecal morphine group, and the hospital length of stay was significantly shorter (3.0 ± 0.5 days vs 3.5 ± 0.7 days; $P = 0.03$). Adverse events did not significantly differ between the groups.

Conclusion: The efficacy of intraoperative intrathecal morphine for postoperative analgesia in the posterior spinal fusion patient population has been shown previously; however, the pain and analgesic trajectory, including transition to other analgesics, has not previously been studied. Our findings suggest that for many patients, use of intrathecal morphine in addition to routine administration of nonopioid medications facilitates direct transition to oral analgesics in the early postoperative period and earlier routine ambulation and discharge of posterior spinal fusion patients.

Introduction

Posterior spinal fusion (PSF) to correct idiopathic scoliosis is associated with severe postoperative pain. Adequate and safe postoperative analgesia remains challenging and controversial, both among anesthesiologists and surgeons (1–9). Intrathecal opioids have been used to manage postoperative pain in pediatric patients for a wide variety of surgeries (7), including adolescent and adult PSF (3–6,9,10). Although these studies have shown reduction in pain on the first day following intrathecal injection, one of the biggest challenges associated with using intrathecal morphine for PSF is anticipating and managing the substantial increase in pain scores that occurs when the analgesic effect of intrathecal morphine wears off on the first postoperative day (3–6,9,10).

At our institution, the standard of care for postoperative analgesia for adolescents undergoing PSF has been an epidural infusion containing hydromorphone as a sole agent. While this method was shown to provide comparable pain relief as intravenous patient-controlled analgesia (IV-PCA) for these patients (8), there are some disadvantages, including the concern for infection related to presence of a foreign body in the surgical site, the technical difficulties with the epidural pumps which remain a frustration for the bedside nurses, and the common occurrence of serous fluid leaking around the epidural site. A single, intraoperative opioid dose administered via the intrathecal route obviates these problems and offers an alternative strategy for pain relief following spinal fusion.

During the summer of 2014, we developed a clinical protocol for intraoperative administration of intrathecal morphine and postoperative transition to oral analgesics. The impetus for this change in our institution's postoperative pain control regimen for PSF surgery was initiated and supported by one of our pediatric orthopedic surgeons who sought a simpler and efficacious approach to managing pain. The purpose of this retrospective study was to (i) describe postoperative pain outcomes in children who received intrathecal morphine with this new clinical protocol, and (ii) compare these outcomes to those in a group of children who received a previously established clinical protocol with epidural hydromorphone (EPI) during the same period.

Methods

Following approval from the Institutional Review Board at the University of Michigan and waiver of informed consent, we identified patients in our electronic surgical database with a diagnosis of idiopathic scoliosis who had undergone PSF and had received an intrathecal morphine injection between June 2014 and April 2015 (intrathecal morphine [ITM] group). We matched these patients by age (±2 years) and gender to adolescents who had received EPI for PSF during the same period (EPI group). Included were patients aged 10–20 years who were developmentally normal and had an American Society of Anesthesiologists (ASA) physical status I, II, or III. All others were excluded.

For the ITM group, intrathecal morphine was administered in a dose of 12 $\mu g \cdot kg^{-1}$ (max 1000 μg) by or under the supervision of the anesthesiologist immediately after induction of anesthesia and prior to incision.

This dose was based on data from Tripi *et al.*(5), where their moderate dose group (mean 14 $\mu g \cdot kg^{-1}$, range 9–19 $\mu g \cdot kg^{-1}$ of intrathecal morphine) had significantly less respiratory complications and intensive care unit admissions compared to the high-dose group (mean 24 $\mu g \cdot kg^{-1}$, 20 $\mu g \cdot kg^{-1}$ minimum of intrathecal morphine). Postoperatively, all children in the ITM group had an order to receive oral oxycodone (0.1 $mg \cdot kg^{-1}$, max 5 mg) starting at 18 h postintrathecal morphine injection. For children in the EPI group, catheters were placed by the surgeon at the end of the operation and bolused with 5 $\mu g \cdot kg^{-1}$ hydromorphone (maximum dose 200 μg) and 1 $\mu g \cdot kg^{-1}$ of fentanyl (max 50 μg), followed by a continuous infusion of 40–60 $\mu g \cdot h^{-1}$, and patient-controlled bolus doses of 5 μg with a lockout interval of 30 min. This has been our institutional standard practice based on our previous published work (8). General anesthetic technique and administration of IV opioids and benzodiazepines during the perioperative period were at the discretion of the anesthesiologist. After recovery in the postanesthesia care unit, these patients were admitted directly to a general pediatric floor.

Postoperatively, all patients in both groups had orders for IV or oral diazepam as needed (dose of 0.05 $mg \cdot kg^{-1}$ for the first 24 h in the ITM group, then increasing to 0.1 $mg \cdot kg^{-1}$; dose of 0.1 $mg \cdot kg^{-1}$ in the EPI group for all time periods), ketorolac (0.5 mg IV/max 15 mg), and acetaminophen (15 $mg \cdot kg^{-1}$ po) were ordered to be given around the clock throughout the postoperative period. For the EPI group, transition to oral oxycodone occurred upon removal of the epidural, either on postoperative day #2 or #3, at the discretion of the surgeon and the anesthesiologist rounding on the acute pain service.

Trained research assistants reviewed the electronic medical records to record all pain scores (0–10 self-reported numeric rating scale), administration of all opioid and nonopioid analgesics, and opioid antagonists. Additionally, they recorded sedation scores (University of Michigan Sedation Scale, range 0–4 where 4 = unarousable); episodes of nausea, vomiting, and pruritus; administration of antiemetics and antipruritics; use of supplemental oxygen; time of first oral intake; time of hospital discharge; and evidence of any other adverse events, including admission to the intensive care unit.

Our primary outcomes were pain scores, opioid use after postoperative day 1, and adverse events. Our secondary outcome was length of stay (LOS). Data were analyzed using Statistical Package for the Social Sciences (SPSS) software (v. 21; IBM, New York, NY, USA). Data are presented as *n* (%) or mean ± standard deviation (SD) as appropriate. Nominal data were compared between ITM and EPI groups using chi-square analyses and parametric data, with unpaired *t*-tests. Pain intensity scores were treated as interval data and compared between groups at specific time intervals using unpaired *t*-tests. Additionally, these data were restructured and a linear mixed model analysis using the maximum likelihood estimation was used to compare the repeated measure, pain intensity score, over time. *P* values <0.05 were considered significant and Bonferroni corrections applied where applicable (e.g., repeated measures).

Results

Twenty patients received intrathecal morphine during the study period. Twenty of 38 patients who received EPI from the same time period were matched to the patients in the ITM group, giving a total sample size of 40 patients. Demographic and surgical characteristics are shown in table 1. The perioperative analgesics administered are depicted in Table 2. The mean dose of morphine used in the ITM group was 11.3 $\mu g \cdot kg^{-1} \pm 1.2$. The concentration of the hydromorphone infusion in the EPI group was 5 $\mu g \cdot ml^{-1}$ for 19 of the patients and 10 $\mu g \cdot ml^{-1}$ for one patient, and the mean rate was 5.1 ± 5.3 $ml \cdot h^{-1}$ with patient-controlled bolus doses of 0.88 ± 0.94 ml. Epidural infusions ran for 30.5–45.57 h (mean 42.0 8 ± 3.64), after which time oral oxycodone was initiated. All patients who received intrathecal morphine were successfully and directly transitioned to oral oxycodone on the first postoperative day without the need for IV opioid rescue.

Pain and analgesic outcomes

Table 3 presents the postoperative analgesics received by children in the ITM and EPI groups. Oral morphine equivalents were significantly lower for children in the ITM group on day 2, but were similar thereafter depicts the means of the highest and lowest recorded pain scores of the two groups over the first three postoperative days, and Table 4 presents the mean differences (95% confidence intervals) over time. When corrected for multiple comparisons, the IT group reported pain scores that were significantly lower only in the postanesthesia care unit (PACU; $P = 0.001$) and higher during the 24–48 h postoperative period ($P = 0.037$). Overall, the linear mixed model demonstrated a significant effect of time on pain scores ($F = 4.28$ (df 1); estimate 0.269 [95% confidence interval 0.010, 0.529], $P = 0.042$), but no effect of Group ($F = 2.35$ (df 1); estimate −0.83 [95% CI −1.93, 0.26], $P = 0.132$). The overall estimated marginal

Table 1 Demographics and surgical characteristics of the groups

	Intrathecal morphine (n = 20)	Epidural hydromorphone (n = 20)	
Age (years)	13.3 ± 2.3 (range 10–20 year)	13.5 ± 1.7 (range 10–17 year)	
Male	2 (10%)	2 (10%)	
Weight (kg)	55.6 ± 15.1	58.0 ± 15.3	
ASA 1/2/3	7 (35%)/13 (65%)/0	8 (40%)/10 (50%)/2 (10%)	
Number of spinal levels fused (median)	9.5 (range 6–12)	10 (range 7–12)	0.281 [−0.730, 0.448], 0.621
Major preoperative curve magnitude (degrees)	55.7 ± 9.3	55.2 ± 11.0	0.193 [−0.583, 0.229], 0.372
Length of surgery (minutes)	264.65 ± 57.61	252.80 ± 46.53	11.85 [−21.72, 45.42], 0.479

Data presented as mean ± SD and n (%).

Table 2 Intravenous analgesics administered during and immediately after surgery in the intrathecal morphine (ITM) and epidural (EPI) groups

	Intraoperatively		Postanesthesia care unit	
Drug	ITM	EPI	ITM	EPI
Sufentanil (n [%])	0	15 (75%)	N/A	N/A
	P < 0.001; 4 [1.872, 8.545]			
Remifentanil	12 (60%)	4 (20%)	N/A	N/A
	P = 0.022; 0.167 [0.041, 0.686]			
Dexmedetomidine	13 (65%)	14 (70%)	N/A	N/A
	P = 1.000; 1.256 [0.334, 4.733]			
Fentanyl	20 (100%)	17 (85%)	1 (5%)	5 (25%)
	P = 0.231; 1.176 [0.979, 1.414]		P = 0.182; 6.333 [0.667, 60.163]	
Morphine (IV)	0	0	1 (5%)	0
			P = 1.000; 0.950 [0.859, 1.050]	
Hydromorphone (IV)	0	2 (10%)	0	1 (5%)
	P = 0.487; 1.111 [0.960, 1.286]		P = 1.000; 1.053 [0.952, 1.164]	
Acetaminophen (IV) (mg·kg^{-1} ± SD)	16 (80%)	16 (80%)	1 (5%)	5 (25%)
	11.0 ± 6.0	11.0 ± 9.0	0.60 ± 2.67	3.32 ± 6.09
	P = 1.000; 0.818 [0.236, 2.835]		P = 0.182; 6.333 [0.667, 60.163]	
Ketorolac	17 (85%)	13 (65%)	4 (20%)	3 (15%)
	P = 0.273; 0.328 [0.071, 1.518]		P = 1.000; 0.706 [0.136, 3.658]	
Diazepam	3 (15%)	12 (60%)	6 (30%)	12 (60%)
	P = 0.008; 8.500 [1.861, 38.817]		P = 0.111; 3.500 [0.945, 12.966]	
Ketamine	2 (10%)	2 (10%)	0	0
	P = 1.000; 1.000 [0.127, 7.893]			
Midazolam (IV)	16 (80%)	18 (90%)	0	0
	P = 0.661; 2.250 [0.362, 13.971]			
Nalbuphine	0	0	1 (5%)	1 (5%)
			P = 1.000; 1.000 [0.058, 17.181]	

Data presented as n (%) or mean ± SD; P value; odds ratio [95% confidence interval].

mean high pain score for the ITM group was 4.38 [95% CI 3.59, 5.17] compared to 5.22 [95% CI 4.43, 6.00]; P = 0.132. The documented time to ambulation was statistically earlier in the ITM group (21.8 ± 5.5 vs 28.8 ± 12.2 h; P = 0.028), as was the documented time of Foley catheter removal (21.5 ± 8.1 h vs 40.5 ± 13.1 h; P < 0.001). In addition, the hospital length of stay was significantly shorter in the ITM group (3.0 ± 0.5 days vs 3.5 ± 0.7 days; P = 0.03).

Opioid-related adverse events

Adverse events during patients' hospital stay are shown in Table 5. Both groups experienced similarly high rates of nausea/vomiting and pruritus. Two patients in the ITM group were admitted to the pediatric intensive care unit for closer neurological and blood pressure monitoring following transient loss of transcranial electric motor-evoked potentials (MEPs)

Table 3 Total postoperative intravenous and oral analgesic doses ($mg \cdot kg^{-1} \cdot day^{-1}$) in the intrathecal morphine (ITM) and epidural (EPI) groups

	Day 1		Day 2		Day 3	
	ITM	EPI	ITM	EPI	ITM	EPI
Oral morphine equivalents	N/A	N/A	0.19 ± 0.07	0.06 ± 0.06	0.16 ± 0.08	0.19 ± 0.07
			<0.001; 0.128 [0.088, 0.167]		0.301; −0.024 [−0.071, 0.023]	
Intravenous diazepam	0.12 ± 0.07	0.14 ± 0.08	0.18 ± 0.09	0.23 ± 0.10	0.18 ± 0.12	0.18 ± 0.11
	0.443; −0.019 [−0.070, 0.031]		0.105; −0.051 [−0.112, 0.011]		0.987; −0.001 [−0.077, 0.076]	
Oral acetaminophen	33.62 ± 12.77	19.67 ± 13.88	42.05 ± 18.05	32.74 ± 13.82	36.21 ± 18.35	34.44 ± 13.70
	0.002; 13.945 [5.298, 22.593]		0.075; 9.306 [−1.009, 19.620]		0.736; 1.771 [−8.721, 12.263]	
Intravenous ketorolac	0.93 ± .29	0.94 ± 0.38	0.77 ± 0.50	1.01 ± 0.38	0.08 ± 0.27	0.10 ± 0.18
	0.952; −0.006 [−0.221, 0.208]		0.094; −0.239 [−0.521, 0.043]		0.853; −0.014 [−0.163, 0.136]	

Data presented as mean ± SD; *P* value; mean difference [95% confidence interval].

Table 4 Mean differences in numeric rating scale (NRS) pain scores (0–10) for children in the intrathecal group (vs epidural group) for the first 3 days

	Highest NRS pain score difference	Lowest NRS pain score difference
PACU	−4.26 (−6.56, −1.96), 0.001	−3.12 (−4.66, −1.57), <0.001
0–8 h	−1.88 (−3.84, 0.82), 0.060	−1.95 (−3.25, −0.66), 0.006
8–16 h	−0.96 (−2.65, 0.73), 0.251	−2.04 (−3.50, −0.59), 0.008
16–24 h	0.018 (−1.55, 1.59), 0.981	−0.85 (−2.16, 0.45), 0.193
24–48 h	1.60 (0.10, 3.10), 0.037	−0.11 (−1.33, 1.10), 0.851
48–72 h	−0.56 (−2.10, 0.99), 0.471	−0.26 (−1.43, 0.91), -.654

PACU, postanesthesia care unit.
Data presented as mean difference; [95% confidence interval of the difference], *P* value for univariate comparisons (not corrected).

Table 5 Adverse events throughout hospital stay in the intrathecal morphine (ITM) and epidural (EPI) groups

Adverse event	ITM	EPI
Postoperative nausea or vomiting	18 (90%)	16 (80%)
Pruritus	8 (40%)	13 (65%)
Use of nasal cannula oxygen	7 (35%)	7 (35%)
Over sedation (per chart notes)	0	3 (15%)
Unplanned admission to intensive care unit	2 (10%)	0

Data presented as *n* (%).

intraoperatively. Both of these patients received norepinephrine and fluid boluses to maintain the mean arterial blood pressure above 70 mmHg, per surgical request following loss of MEPs intraoperatively. The first patient received 740 μg intrathecal morphine ($11.8\ \mu g \cdot kg^{-1}$) and a length of surgery 422 min. While in the PICU, this patient received 2 l of normal saline bolus and had a norepinephrine infusion ($0.0\ 1\ mg \cdot kg^{-1} \cdot min^{-1}$) for a total of 2.5 h. The second patient had received 600 μg intrathecal morphine ($11.5\ \mu g \cdot kg^{-1}$), and a length of surgery of 341 min. This patient was also started on a norepinephrine infusion (titrated to a max of $0.05\ mg \cdot kg^{-1} \cdot min^{-1}$) for about 9 h, in addition to receiving a total of 3 l crystalloid bolus while in the PICU. Both of these children were discharged home without any neurologic deficits.

One-third of children in both groups required nasal cannula oxygen to maintain SpO_2 >92% at some point after PACU discharge; however, none required naloxone or additional treatment for hypoxemia. All patients in both the ITM and EPI groups received at least two antiemetic drugs intraoperatively, usually ondansetron and dexamethasone, and many received diphenhydramine as a third agent. Despite this, based on rates of administration of antiemetics, the incidence of postoperative nausea and vomiting was 90% in the ITM group and 80% in the EPI group ($P = 0.661$). One patient from the EPI group required straight catheterization for urinary retention after the epidural was removed. No incidence of postdural puncture headache was noted for either group.

Discussion

The efficacy of intraoperative administration of intrathecal morphine for postoperative analgesia in the PSF patient population has been shown previously (3–6,9,10). However, the pain and analgesic trajectory, including transition to oral analgesics, has not been previously studied and has remained a challenge. Our findings suggest that in our setting, use of intrathecal morphine in addition to routine administration of nonopioids facilitated direct transition to oral analgesics in the early postoperative period with effective analgesia that facilitated early ambulation and discharge.

Not surprisingly, intrathecal morphine appeared to be most effective in controlling pain during the first 16 h postoperatively. After this point, pain scores

significantly increased for the ITM group compared to the EPI group, which had relatively stable pain scores over time. Importantly, our routine practice is to administer the first rescue opioid at 18 h from the time of the intrathecal morphine injection. Although directly transitioning from intrathecal morphine to oral oxycodone at 18 h facilitated adequate analgesia for the majority of children, the reported spike in pain scores after this transition suggests that children may not have been well-prepared that the intrathecal morphine effects would wear off. Our protocol does emphasize postoperative use of nonopioids (acetaminophen and ketorolac) around the clock to help facilitate analgesia during and after this transition.

While our rates of nausea and vomiting were high in the ITM group, they were nearly as high in our EPI group, suggesting that both routes of opioid administration are similarly associated with this adverse effect. These rates are higher than those published in other studies of intrathecal morphine (3,5), but similar to prospective studies where children are asked directly about nausea (9). It may be that our clinicians assess and treat this effect more readily than in other settings. Our reported rates of nausea were inferred from the administration of antiemetic drugs by nursing staff, and it is possible that in some cases, antiemetics were given in a prophylactic fashion, thus artificially increasing our reported rates of nausea. Nonetheless, it is clear that management of this very troublesome side effect in this high-risk patient population could be improved.

No serious adverse outcomes were noted in terms of persistent neurologic deficits or respiratory depression requiring intervention beyond nasal cannula oxygen. Thirty-eight patients were managed in general pediatric care units postoperatively; two patients were admitted to the PICU for close neurovascular monitoring due to transient loss of transcranial electric MEPs intraoperatively. Both of these patients required vasopressors for blood pressure augmentation. It is possible that the use of intrathecal morphine at the doses we used increased the risk for hypotension compared to other methods of analgesia. Adequate fluid resuscitation for these patients is difficult, given the relatively high blood loss associated with PSF concurrent with the desire to avoid high-volume crystalloid resuscitation as it is associated with increased risk for postoperative visual loss in these surgeries (11–13). Nonetheless, it remains important to recognize, monitor for, and intervene to prevent or treat hypotension when intrathecal morphine is used during PSF.

Notably, intrathecal morphine was associated with a decreased length of stay in this small sample of children. It is possible that this is related to superior postoperative pain control in the early postoperative period, which better facilitated physical therapy and mobility. Earlier Foley catheter removal and ambulation in the ITM group may have been related, in part, to the absence of an epidural catheter and pump, and this may also have contributed to a shorter hospital stay. The multidisciplinary care plan for PSF patients in our setting has now incorporated earlier mobility goals and expectations given the ITM protocol, and planned discharge on postoperative day 2 is now thought to be achievable for many patients who transition to orals with adequate pain control.

The ability to generalize our data is limited by the retrospective nature of this study and the possibility of confounding, undocumented factors. We cannot overlook the possibility of reporting bias as our data were extracted from nursing and medical records where underreporting of adverse events is likely. Additionally, our use of medication administration as a proxy for adverse events may have resulted in an overestimation of events as nurses often administer these agents prophylactically. Lastly, given our small sample size, it is quite likely that this study was underpowered to detect differences in some of our outcomes such as adverse events. Therefore, further study in a larger sample is warranted.

In summary, intrathecal morphine, in conjunction with adequate nonopioid adjuvants, was well tolerated and facilitated direct transition to oral analgesics in the early postoperative period in our small sample size of adolescents who underwent PSF for idiopathic scoliosis.

Ethics approval

This study was approved by University of Michigan IRB, ID: HUM00094624, February 16, 2015.

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Conflict of interest

The authors report no conflict of interest.

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