

Systematic Review: A Systematic Review of Studies on the Outcome and Side Effects of Intrathecal Morphine Injection in Posterior Fusion Surgery of Patients with Idiopathic Scoliosis

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ABSTRACT

The present study is a systematic review on the results and complications of intrathecal morphine injection in posterior fusion surgery of patients with idiopathic scoliosis. Scoliosis is a lateral curvature of the spine. Considering that complications after surgery are common in these patients, the present study was conducted with the aim of investigating the complications after posterior fusion surgery with instruments in adult patients with scoliosis of unknown cause. Most studies administered morphine under direct administration at the end of the procedure and before wound closure. In the present study, we administered morphine in the operating room before surgery and demonstrated the possibility of prophylactic analgesia through ITM at a dose of 0.3 mg. In a double-blind trial investigating prophylactic analgesia with low-dose intra spinal morphine in multilevel posterior-lumbar inter body fusion surgery, Wang et al. showed that prophylactic analgesia with intra spinal morphine led to a significant improvement in postoperative pain control and a reduction in the use of intrathecal analgesia. The vein is under the control of the patient after the operation, without increasing side effects. Patients undergoing lumbar spine surgery may experience significant pain in the early postoperative period, and poor pain control after multilevel lumbar spine fusion surgery is often associated with multiple complications and delayed hospital discharge. Posterior spine surgery can result in severe postoperative pain due to the extensive soft tissue incision and muscle dissection required to obtain adequate exposure of the laminae, facet joints, and transverse processes.

Introduction

Administering an analgesic before the pain stimulus occurs can prevent pain hypersensitivity. There are many interventions for potential use as prophylactic analgesia in

lumbar spine surgery, including epidural analgesia, wound infiltration with local anesthesia, systemic opioids, and systemic nonsteroidal anti-inflammatory drugs (37-40). Analgesia caused by ITM is carried out by pre- and post-synaptic receptors in the gelatinous

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substance of dorsal horn cells of the spinal cord and supra spinal surfaces (1). The present study investigated the issue by reviewing more than 35 articles with keywords including

"Intrathecal morphine injection", "Posterior fusion surgery", "Patient", "Idiopathic scoliosis". (Figure 1).

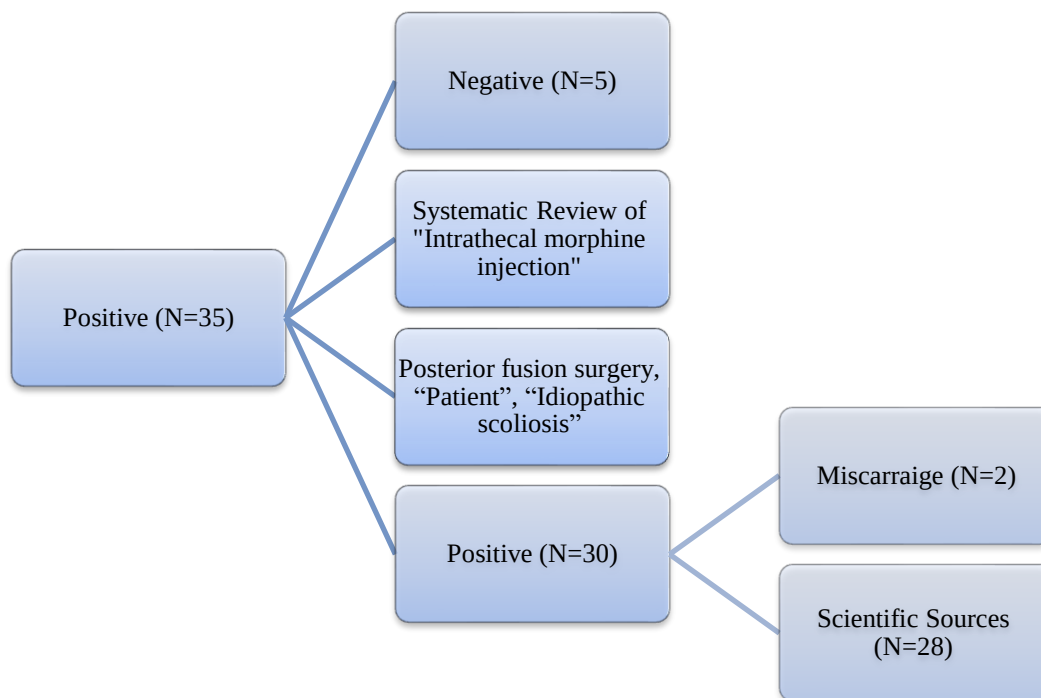


Figure 1. Flow chart of included subjects

In a retrospective cohort study, Milbrandt et al. in 2008 in the United States compared three pain control methods for posterior spinal fusion in adolescent idiopathic scoliosis. To compare the efficacy of patient-controlled analgesia (PCA) with morphine alone, an intrathecal morphine injection and PCA (IT/PCA), and an epidural catheter injection without PCA (EPI) for pain control after posterior spinal fusion (PSF) surgery and segmental spinal instrumentation (SSI) was performed in adolescent idiopathic scoliosis (AIS). Postoperative pain control after PSF and SSI in AIS can be managed in different ways. EPI provides a longer duration of pain relief, but relies on proper placement and maintenance of the catheter in the epidural space.

A preoperative intrathecal morphine injection also provides extended duration. No direct comparison of these 3 methods of postoperative pain control has been reported. An IRB-approved retrospective chart review was conducted at 2 institutions from 1997 to 2005. Medical records were reviewed to determine postoperative pain scores at multiple time points. 3 groups were significantly compared using Student's t test and χ^2 , $P < 0.05$. There was no statistical difference in gender, age, magnitude of the curve or the number of combined levels. The IT/PCA group was 42 patients, the PCA group was 41 patients, or the EPI group was 45 patients. Postoperative pain scores in the IT/PCA group were the lowest in the first 8 hours ($P < 0.05$), but were lower in the EPI group after 24 hours ($P < 0.05$). Total morphine consumption (mg/kg) was lower in IT/PCA.

The group was compared with the PCA group at 12 hours and 24 hours ($P=0.0001$). Return to solid food consumption was faster in EPI group (2.0 days) followed by IT/PCA (2.6 days) and PCA alone (3.2 days) ($P<0.002$). More transient neurological changes occurred in the EPI group (11.55, EPI IT/PCA 1.42, PCA 41.0 $P<0.001$). The highest amount of itching was in the epidural group ($P<0.05$, 11.55).

In none of the groups, there was any change or permanent nerve damage or sensory-somatopotential stimulation during the operation. The results showed that the EPI group controlled postoperative pain for the longest period of time and allowed a faster return to normal food consumption. However, a preoperative intrathecal morphine injection provides equal pain control for the first 24 hours with less itching and fewer side effects. Therefore, it requires less intervention by nurses and doctors after PSF and SSI in AIS. All procedures were safe with no documented neurological damage (2).

In a 2020 study in India, Ye et al investigated methadone-based multimodal analgesia for best acute surgical pain control and functional outcomes with less opioid consumption following large posterior fusion surgery in adolescents with idiopathic scoliosis. Posterior spinal fusion in idiopathic scoliosis is very painful without analgesia. A methadone-based multimodal analgesia protocol was used with the aim of reducing hospital length of stay (LOS), improving pain control and reducing the need for additional opioids. 122 idiopathic scoliosis patients with posterior spinal fusion were studied.

They were matched by age, sex, surgeon, and number of combined levels before and after implementation of the new protocol. This analysis included 61 patients in the control group (intra spinal morphine, gabapentin, intravenous opioids and adjuvants) and 61 patients in the new protocol (scheduled

methadone, methocarbamol, ketorolac/ibuprofen, acetaminophen and oxycodone with narcotics). Intravenous as narcotics was required).

The primary outcome showed that secondary outcomes including pain scores, total opioid consumption (mg morphine equivalents), time to first bowel movement, and post-discharge telephone calls (median LOS, 2 days) compared with control patients (3 days ($P<0.001$)) was less. Also, the total consumption of inpatient morphine was lower in the protocol group ($P>0.001$). Pain scores in the protocol group were higher on the day of surgery, on the 1st postoperative day (POD), and were lower on the 2nd POD ($P=0.01$). The new protocol also reduced the mean time to first bowel movement ($P<0.001$) and the number of pain-related telephone calls after discharge ($P<0.006$).

The results of the study showed that methadone-based multimodal analgesia resulted in a significant reduction of LOS compared to the conventional regimen. It also improved pain control, reduced total opioid consumption, and early bowel movement compared to the control group (3).

In a 2020 study in the United States, Li and his colleagues investigated safe and effective intrathecal morphine and oral analgesics for pain control after posterior spinal fusion in adolescent idiopathic scoliosis patients. In this study, patients aged 10 to 17 years who underwent PSF were identified and 28 patients who received intrathecal morphine were compared with 28 patients who received hydromorphone EPI. Intrathecal morphine group received oral oxycodone starting 16 hours after injection.

The EPI group received oxycodone after removal of the epidural catheter on the second postoperative day. Pain scores, side effects and length of hospitalization were recorded. A large number of EPI patients received fentanyl

($P=0.014$ vs. 11) in the post-anesthesia care unit (PACU). The intrathecal morphine group had lower pain scores between PACU discharge and midnight ($P=0.034$ mean 4.2 versus 2.9). Pain scores were similar during the remaining postoperative periods.

All patients on intrathecal morphine without intravenous opioids were switched to oxycodone. Movement time (26.5 vs. 19.9 hours, $P=0.010$) and Foley catheter removal (21.3 vs. 41.9 hours, $P<0.001$) were earlier in intrathecal morphine patients. The results showed that the duration of hospitalization in the ITM group was shorter ($P=0.043$, 3.5 days versus 3.1 days) and oral analgesics provided safe and effective pain control after PSF for AIS (4).

In 2015, Ibach and colleagues in Texas investigated the duration of the effect of intrathecal morphine in children with idiopathic scoliosis undergoing posterior spinal fusion. In this study, 44 children with idiopathic scoliosis who received IT morphine after posterior spinal fusion (PSF) were included in the study. The average exposure to opioids was 0-12 hours and 13-24 hours after IT morphine and the average exposure. Exposure to opioids increased significantly during 13-24 hours compared to 0-12 hours (23.0 ± 12.5 mg vs 15.9 ± 1.7 mg of injected morphine) ($P=0.0006$). The results showed that patients improved at least 12 hours after intrathecal morphine.

Increased use of adjunctive analgesics such as acetaminophen may reduce the need for opioids following PSF procedures. Further studies are needed to investigate the combination of adjuvants and intrathecal morphine to reduce postoperative pain in this population (5).

In a 2014 retrospective study in the United States, Hong et al investigated intrathecal morphine and epidural hydromorphone in analgesia following posterior spinal fusion in

adolescents with idiopathic scoliosis. In this study, children aged 10 to 20 years old with a diagnosis of idiopathic scoliosis who underwent elective posterior spinal fusion surgery from June 2014 to April 2015 were identified from an electronic database (6). For the intrathecal morphine group, a dose of 12 mg/kg (maximum 1000 mg) is prescribed before cutting. Postoperatively, all children in the intrathecal morphine group were instructed to receive oral oxycodone (0.1 mg/kg, maximum 5 mg) starting 18 hours after the intrathecal morphine injection. For the epidural hydromorphone group, catheters were placed by the surgeon and bolus with 5 L/kg hydromorphone (maximum 200 mg) and 1 mg/kg fentanyl (maximum 50 mg) followed by a continuous infusion of 40 to 60 mg/h. 1 Patient-controlled bolus doses of 5 mg with a 30-minute lock-in interval.

All patients in both groups had acetaminophen, diazepam and ketorolac after the operation (7). During the study period, 20 patients received intrathecal morphine and were matched with 20 patients who received epidural hydromorphone.

All patients in the intrathecal morphine group were transferred to oral analgesics on the first postoperative day without the need for intravenous opioids after discharge from the post-anesthesia care unit. Compared to the epidural hydromorphone group, the intrathecal morphine group reported lower pain scores in the post-anesthesia care unit (mean difference -4.62, confidence interval ($P=0.001$, -1.96, -6.56) 95% CI, the first 8 hours after surgery (difference in mean -1.88 ($P = 0.060$ 95% CI, -0.082, -3.84)) and higher pain scores on the second day after surgery, the difference in the average recorded time until discharge and Foley catheter removal were statistically earlier in the intrathecal morphine group and the duration of hospitalization was significantly shorter (3 ± 0.5 days vs. 3.5 ± 0.7

days; $P=0.03$). The side effects did not differ significantly between the groups (8). The results showed that in many patients, the use of intrathecal morphine, in addition to the routine administration of non-narcotic drugs, led to a direct transition to oral painkillers. It facilitates the post-operative period and routine setup and discharge of posterior spinal fusion patients (9).

In a study conducted by Mindy Cohen and colleagues in 2016 in the United States, they investigated intrathecal morphine compared to epidural morphine with long-term analgesia for postoperative pain control in pediatric patients undergoing posterior spinal fusion. 71 patients were examined (10). Posterior spinal fusion for idiopathic scoliosis completed the study. The groups were randomly divided into two groups of $7.5\mu\text{g/kg}$ morphine, intrathecal morphine or $150\mu\text{g/kg}$ epidural morphine. The last group of intrathecal morphine and epidural morphine treated postoperative pain with morphine PCA, ketorolac, oral oxycodone and acetaminophen. Morphine consumption, pain scores, nausea and vomiting, itching and respiratory distress were measured every 4 hours (11). Epidural morphine and intrathecal morphine groups had no difference in time to first PCA demand. Pain scores between 8 and 24 hours after surgery did not differ between groups. Compared with intrathecal morphine, epidural morphine subjects had lower pain scores from 28 to 36 hours after surgery. The incidence of reported pruritus was lower in epidural morphine subjects. There was no difference in total morphine consumption or time to first PCA demand between the epidural morphine and intrathecal morphine groups. The results of the study showed that epidural morphine provides a longer duration of analgesia after posterior spinal fusion for scoliosis and may be associated with less opioid-induced itching (12).

In a 2012 retrospective case-comparison study in America, Ravish et al investigated pain management in adolescent idiopathic scoliosis patients undergoing posterior spinal fusion with combined treatment of continuous intrathecal and epidural morphine compared to PCA. Efficacy and safety of combined intrathecal morphine (ITM) (13) and epidural analgesia (EPI) (14) with patient-controlled conventional intravenous analgesia (IV-PCA) after posterior spinal fusion (PSF) for adolescent idiopathic scoliosis (AIS) (15) compared. Pain control after PSF in AIS has traditionally been managed with IV-PCA. Recent studies have shown improvement in pain control using continuous EPI or intraoperative ITM (16). No study has compared the use of ITM and EPI analgesia with IV-PCA. A case-control study was conducted from 1989 to 2009 for patients undergoing PSF for AIS. Patients received IV-PCA or ITM/EPI. Daily pain scores along with total opioid and benzodiazepine consumption and side effects were recorded for all patients. A total of 146 patients were studied, initially 95 patients received ITM/EPI and 51 patients received IV-PCA as controls (17).

Eight patients from the ITM/EPI group were excluded from the pain comparison part of the study. There was no statistical difference in age, sex, weight or hospitalization between the 2 groups. The ITM/EPI group had an average of 1 additional level of fusion ($P=0.001$). The average daily pain scores in the ITM/EPI group were lower on all hospitalization days and were statistically lower on days 1 and 3 to 5 (18). Overall opioid requirements were significantly lower in ITM/EPI patients, although oral opioid consumption was higher in this group. Total benzodiazepine consumption was lower in the IV-PCA group. In total, 15.7% of IV-PCA patients had bladder hypotonia, compared to 1.1% of the ITM/EPI group ($P=0.002$). The rate of ileus in V-PCA

patients was 15.7% and in ITM/EPI patients was 5.7% ($P=0.071$). The result of the study showed that the use of ITM/EPI after PSF is safe and effective, this method significantly reduces the total consumption of opioids and pain scores. It can lead to urinary and bowel dysfunction (19).

In a retrospective case-comparative study in the investigation of pain management in adolescent idiopathic scoliosis patients undergoing posterior spinal fusion with continuous intrathecal and epidural morphine treatment compared to PCA, they showed the average daily pain scores in the ITM/EPI group. It was lower in all days of hospitalization and it was statistically lower in days 1 and 3 to 5. The overall need for opioids was significantly lower in ITM/EPI patients, although oral opioid consumption was higher in this group. The rate of ileus was 15.7% in V-PCA patients and 5.7% in ITM/EPI patients ($P=0.071$). The results of the study showed that the use of ITM/EPI after PSF for AIS is safe and effective, this method significantly reduces the total consumption of opioids and pain scores, which can lead to urinary and bowel dysfunction (20).

Milbrandt et al. compared three methods of pain control for posterior spinal fusion in adolescent idiopathic scoliosis and showed that the EPI group controlled postoperative pain for the longest period of time (21) and allowed a faster return to eating normal foods. Preoperative intrathecal morphine injection provides equal pain control in the first 24 hours with less itching and fewer side effects. Therefore, it requires less intervention by nurses and doctors after PSF and SSI in AIS. All procedures were safe with no documented neurological damage (23). In our study, the average time of first oral intake in patients without intrathecal morphine injection (5.8 ± 1.0 hours) was less than the average time of first oral intake in patients without

intrathecal morphine injection (17.7 ± 10.3 hours) (22).

Ibach et al., in investigating the duration of the effect of intra spinal morphine in children with idiopathic scoliosis undergoing posterior spinal fusion, showed that the patients improved at least 12 hours after intra spinal morphine. Increased use of adjunctive analgesics such as acetaminophen may reduce the need for opioids following PSF procedures (26). The results of this study are in line with our study. Because in the group with intrathecal morphine injection, the need to request pain medication was less (23).

Previous studies on the use of ITM in spine surgery have shown that ITM is an effective method for pain management and spine surgery has shown that ITM is an effective method for pain management and reducing postoperative complications in PSF patients recovering from surgery (24).

Some studies have shown that intra spinal morphine and epidural hydromorphone in analgesia following posterior spinal fusion in adolescents with idiopathic scoliosis, the use of intra spinal morphine in addition to the routine administration of non-narcotic drugs, direct transfer to oral analgesics in the early period after facilitates the routine operation and discharge of posterior spinal fusion patients (25).

The results of our study are consistent with the results of previous studies, because in our study, on average, pain medication was requested every 7 hours in patients without intrathecal morphine injection and every 3 hours in patients without intrathecal morphine injection ($P<0.05$).

Also, there was a significant difference in the average duration of hospitalization in patients with and without intrathecal morphine injection after posterior fusion surgery of patients with idiopathic scoliosis (P -Value <0.05). Thus, the average duration of

hospitalization in patients with intrathecal morphine injection (4.8 ± 1.0 days) was less than the average duration of hospitalization in patients without intrathecal morphine injection (7.7 ± 1.3 days) (26).

Patients, hospitals, and insurance companies benefit from the routine use of ITM because reduced length of stay and early discharge reduce health care costs at each care facility (27).

Posterior spinal fusion in idiopathic scoliosis appears to be very painful without analgesia. Prophylactic ITM significantly reduced the need for sedation on the first day after lumbar spine surgery. Despite these positive findings regarding the introduction of ITM (28) as an intrathecal injection method after spine surgery, the routine use of ITM is still not standard practice in many practice centers. In a prospective, randomized, single-blind study of patients with AIS undergoing PSF comparing high-dose and high-dose ITM, Eschertzhuber et al showed that high-dose ITM resulted in a reduction in estimated blood loss per patient. (EBL) and requirements of opioid substances after surgery (29).

Other studies evaluating the use of splints during scoliosis surgery have shown that EPI provides pain relief for the longest postoperative period while allowing for a faster return to solid foods. he does. Ravish et al found

that an ITM/EPI combination is a safe and effective method for pain management in patients with AIS undergoing PSF, and that the ITM/EPI combination significantly reduced pain and reduced total opioid consumption (30). This study confirms previous findings that routine intraoperative use of ITM reliably reduces postoperative opioid use. The introduction of ITM leads to a reduction in opioid exposure for patients, possibly reducing the likelihood of postoperative dependence. Based on the results of this study and several other previously published studies, we recommend that scoliosis surgeons consider the use of ITM in their standard operating protocols. (29).

The main limitation of clinical use of ITM may be side effects caused by morphine use such as nausea, vomiting, itching and urinary retention (Table 1). Pruritus is a particular complication of opioids. In the present study, three patients in the group with intrathecal morphine injection had itching side effects. In some studies, the incidence of itching with epidural or intravenous morphine has been reported to be 28 to 75% (2). However, the incidence of pruritus in our study was very low, and there was no significant difference between the two groups in the incidence of other morphine-related adverse events (30).

Table 1. Forest plot showed the Application of Robotic Instruments in Hip Arthroplasty Surgery Based on Practical Tips a Systematic Review

Raw	Study	Year		Proportion Wight 98%		Weight %
1	Cousins et al.	1984		0.68	[0.52 – 1.06]	6.02
2	Fournier et al.	2000		0.74	[0.31 – 1.08]	5.92
3	Roy et al	2006		0.89	[0.19 – 1.01]	5.65
Heterogeneity t²=0.00, I²= 0.02, H²=1.01				0.98	[0.20 – 1.06]	
Test of θ= θ, Q (4) =4.00, P= 0.71						

1	Hida et al.	2016		0.92	[0.39 – 1.06]	5.03
2	Pendi et al.	2018		0.87	[0.54 – 1.02]	6.02
3	Tripi et al.	2015		0.88	[0.63 – 1.01]	5.57
Heterogeneity $t^2=0.02$, $I^2= 0.03$, $H^2=1.02$				0.95	[0.22 – 1.07]	
Test of $\Theta= \Theta$, $Q (4) =2.09$, $P= 0.74$						
1	Fletcher et al.	2014		0.84	[0.27 – 1.08]	6.08
2	Eschertzhuber et al.	2008		0.76	[0.36 – 1.06]	5.82
3	Ravish et al.	2012		0.69	[0.28 – 1.05]	5.85
Heterogeneity $t^2=0.01$, $I^2= 0.04$, $H^2=1.03$				0.095	[0.29 – 1.06]	
Test of $\Theta= \Theta$, $Q (4) =4.09$, $P= 0.40$						

Conclusion

Morphine contains hydroxyl groups that, as a hydrophilic opioid substance, give it polar characteristics, thereby reducing the permeability of biological membranes and delaying the absorption of cells and blood. Therefore, ITM has a longer duration of action and a faster onset than other opioids. The onset of analgesia appears to occur approximately 30 minutes after ITM injection, and an ITM bolus is estimated to have an onset of 1 to 2 hours and a duration of 12 to 24 hours. Intrathecal morphine injection leads to a significant reduction of postoperative pain and reduction of oxygen use, reduction of the need for narcotic drugs, and reduction of the average time of the first oral administration, and increases the hours of painkiller request, but leads to an increase in nausea, itching and side effects in 24 hours after the operation.

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