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The Effect of Preoperative, Low-Dose Intrathecal Morphine on Patient Outcomes Following Lumbar Fusion Surgery: Can We Teach an Old Dog New Tricks?

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ABSTRACT

Background: Early pain control after lumbar fusion presents a challenge to patients and providers. Intrathecal morphine (ITM) has been used at the end of these procedures with limited benefit, but recent data suggest low-dose ITM at case initiation may be effective. This study aims to evaluate the use of preoperative ITM during lumbar fusion to determine whether there is a benefit for these patients.

Methods: One hundred and eighty lumbar fusion patients between 1 January 2018 and 31 May 2022 were evaluated. Patients were grouped by whether they received preoperative, low-dose ITM or not. Outcomes of interest included hospital narcotic consumption, pain scores, opioid-related complications, and complications within the first 90 days.

Results: Sixty-five study patients received 200 μg ITM at case initiation and 115 did not. No differences in length of stay, discharge disposition, or complications in the first 90 days were noted. ITM patients received fewer milligram morphine equivalents in the postanesthesia care unit (9.7 ± 31.23 vs 21.83 ± 21.07; $P = 0.006$) and on postoperative day 0 (18.60 ± 35.47 vs 35.47 ± 28.51; $P = 0.001$). Pain scores were lower in the ITM group both in the postanesthesia care unit and on postoperative day 0, with a decrease in extreme pain scores (>7; 35.4% vs 53.0%; $P = 0.034$).

Conclusions: ITM appears to be safe and effective for reducing early pain and narcotic consumption on the day of surgery for lumbar fusion patients and may hold value for incorporation into rapid recovery protocols and for improving pain-related patient satisfaction.

Clinical Relevance: ITM appears to be safe and effective for reducing early pain and narcotic consumption on the day of surgery for lumbar fusion patients and may hold value for incorporation into rapid recovery protocols and for improving pain-related patient satisfaction.

Level of Evidence: 3.

Lumbar Spine

Keywords: intrathecal morphine, lumbar fusion, narcotics, outcomes, pain control

INTRODUCTION

Postoperative pain management is an important component in improving outcomes following lumbar fusion surgery, which can cause significant postoperative pain due to the extensive soft-tissue dissection and muscle detachment required to provide adequate exposure.[1] Various methods of pain management have been utilized to control postoperative pain, particularly in the initial 24–48 hours. Multimodal analgesia (MMA) has been employed in spinal surgery with good outcomes, including reduced opioid prescription and length of hospitalization, decreased gastrointestinal complications, and improved pain control.[2,3] Additionally, MMA has become an important factor in rapid recovery protocols utilized to decrease length of stay (LOS).[4] In comparison to patient-controlled anesthesia (PCA), MMA appears to be an appropriate alternative for fusion surgery in the lumbar spine.[5] Both spinal and regional analgesic techniques have been incorporated as part of MMA models and enhanced recovery protocols. Historically, long-acting intrathecal narcotics, administered at the end of a lumbar decompression, were considered for postoperative pain control but had limited use due to complications including respiratory depression and urinary retention.

Recent studies have revisited the use of lower dose, preoperative intrathecal morphine (ITM). In recent years, ITM use in spinal surgery has increased. Various studies have offered options for optimal ITM dosing for pain management in posterolateral lumbar fusions, with some suggesting 0.3 mg (0.004 mg/kg) administered during the procedure while others recommend 0.25 or

0.5 mg ITM.[6,7] While no standard dose has been determined, there has been evidence of some benefit of ITM in spinal surgery. There has been renewed interest in using ITM in addition to other methods of pain relief, as intrathecal narcotics have been utilized in other surgical specialties with good effect.[8–10] Studies performed on patients undergoing minimally invasive cardiac surgery demonstrated decreased intravenous opioid utilization in the postanesthesia care unit (PACU) and significantly decreased pain scores in those receiving ITM compared with patients utilizing a piritramide PCA.[11] Similarly, patients undergoing major laparoscopic abdominal surgery given ITM utilized less total milligram morphine equivalents (MMEs) and experienced lower pain levels postoperatively.[12] This study aims to evaluate the use of low-dose ITM prior to the initiation of lumbar fusion procedures to determine whether there is a benefit to early pain control. Outcomes such as postoperative pain scores, LOS, complication rates, and readmissions will be compared between groups to determine whether a benefit to early ITM administration is present for lumbar fusion patients.

MATERIALS AND METHODS

Study Population

This study was deemed exempt from institutional review board review by the institutional clinical research committee. Informed consent was not required given this exemption. The institutional review board record number is 1993664. All patients included in this study underwent lumbar fusion between January 2018 and May 2022. A total of 180 patients met the inclusion criteria. Patients who received intrathecal narcotics were matched 1:2 with a cohort that did not receive intrathecal narcotics. Patients were matched on age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) classification, and number of levels fused. Surgeries were performed by 4 board-certified orthopedic spine or neurosurgeons, and all patients were cared for using a coordinated spine surgery pathway in a dedicated spine center. A standard postoperative pain protocol including an opioid, muscle relaxer, acetaminophen (if not included in the opioid), and ketorolac (if not contraindicated) was ordered for all patients regardless of group. All medications in the standard pain protocol were ordered on an as needed basis.

Independent Variables

The electronic medical record was abstracted to obtain patient demographics including age, BMI, race, ASA score, number of levels, intraoperative fentanyl, intraoperative morphine, intraoperative hydromorphone, intraoperative fluid received, total PACU MME, total floor MME, postoperative MME, maximum postoperative pain scores, reinsertion Foley or straight catheter, oxygen saturation, respiratory rate, naloxone use, diphenhydramine or nalbuphine hydrochloride use, and ondansetron or promethazine use.

Outcome Measures

The primary outcomes of interest were LOS, discharge home, 90-day emergency department (ED) return, 90-day readmission, 90-day postoperative complication, and complication type.

Statistical Analysis

Patients were grouped based on whether they had received 200 μg of ITM at the initiation of the case or not. Univariate analysis, including χ^2, and 2-sided independent samples *t* tests, were used to determine differences in patient demographics, medication, pain scores, and adverse events between the 2 groups and the impact of ITM on postoperative outcomes for those who had a lumbar fusion. Urinary retention was defined as the reinsertion of a foley or straight catheter. Respiratory depression was defined as either an oxygen saturation less than 92% after PACU or a respiratory rate less than 10/min after PACU. Oversedation was defined as postoperative naloxone use. Itching was defined as postoperative diphenhydramine or nalbuphine hydrochloride use. Nausea was defined as postoperative ondansetron or promethazine use. Univariate analysis including χ^2 tests and 2-sided independent samples *t* tests were used to determine differences between groups. The Fisher's exact test was performed when the assumptions of χ^2 testing were not met. All statistical analyses were performed using R Studio (version 1.4.1717 2009–2021 RStudio, PBC). Statistical significance was assessed at $P < 0.05$.

RESULTS

Of the 180 lumbar fusion patients, 65 received ITM and 115 did not. There were no differences in age, BMI, sex, ASA score, or number of levels fused after matching. On average, patients were 64 years old with an average BMI of 31. Nearly 60% of patients were men and approximately 40% were women. Roughly, 57% of patients had an ASA score of 3 or more, and 36% of patients had a fusion of 3+ levels (Table 1).

Table 1. Patient demographics.

Demographics	No ITM (n = 115)	ITM (n = 65)	P
Age, y	64.18 ± 12.45	63.88 ± 11.44	0.872
Body mass index	31.72 ± 6.26	31.14 ± 6.25	0.559
Sex			>0.99
Man	67 (58.3)	38 (58.5)	
Woman	48 (41.7)	27 (41.5)	
ASA score 3+	68 (59.1)	35 (53.8)	0.595
Fusion of 3+ levels	36 (31.3)	26 (40.0)	0.309

Abbreviations: ASA, American Society of Anesthesiologists; ITM, intrathecal morphine.
Note: Data are expressed as mean ± SD or *n* (%).

Table 3. Maximum Pain scores.

Pain	No ITM (n = 115)	ITM (n = 65)	P
In PACU	6.78 ± 2.46	5.25 ± 3.62	**0.004**
On POD 0	6.65 ± 2.81	4.58 ± 3.33	**<0.001**
On POD 0 ≥7	61 (53.0)	23 (35.4)	**0.034**
On POD 1	7.48 ± 2.22	6.98 ± 2.67	0.212
On POD 1 ≥7	84 (73.0)	38 (58.5)	0.066
On POD 2	7.39 ± 2.27	7.44 ± 2.62	0.917
On POD 2 ≥7	48 (41.7)	33 (50.8)	0.311
On POD 3	7.71 ± 2.08	8.50 ± 1.77	0.107
On POD 4	8.29 ± 2.03	7.36 ± 1.95	0.171
During hospital stay	8.68 ± 1.75	8.17 ± 2.23	0.120

Abbreviations: ITM, intrathecal morphine; PACU, postanesthesia care unit; POD, postoperative day.
Note: P values < 0.05 in bold. Data are expressed as mean ± SD or *n* (%).

Those who received ITM received, overall, more intraoperative MMEs (90.29 ± 22.93 vs 54.23 ± 35.67; $P < 0.001$); however, once the ITM was excluded for, ITM patients received significantly less intravenous MMEs intraoperatively than those who did not receive ITM (37.41 ± 19.92 vs 54.23 ± 35.67; $P < 0.001$). On average, ITM patients received 54 MMEs of ITM. Additionally, ITM patients received less intraoperative fentanyl (132.50 ± 63.50 μg vs 191.36 ± 130.14 μg; $P < 0.001$), less intraoperative hydromorphone (0.91 ± 0.61 mg vs 1.32 ± 0.85 mg; $P = 0.015$), and more intraoperative morphine (5.83 ± 2.73 vs 2.00 ± 0; $P < 0.001$). There was no difference in total fluid received. Postoperatively, ITM patients received less total MMEs in the PACU (9.7 ± 31.23 vs 21.83 ± 21.07; $P = 0.006$), postoperative day (POD) 0 on the floor (8.86 ± 13.55 vs 13.64 ± 15.63; $P = 0.033$) and in total (floor and PACU) on POD 0 (18.60 ± 35.47 vs 35.47 ± 28.51; $P = 0.001$; Table 2).

When evaluating pain scores, ITM patients had lower overall pain in the PACU (5.25 ± 3.62 vs 6.78 ± 2.46; $P = 0.004$) and on POD 0 (4.58 ± 3.33 vs 6.65 ± 2.81; $P < 0.001$). Additionally, ITM patients were less likely to have a pain score greater than 7 on POD 0 (35.4% vs 53.0%; $P = 0.034$). There were no differences in maximum pain scores on days 1, 2, 3, or 4 or during hospital stay (Table 3).

ITM was not associated with increased rates of urinary retention, respiratory depression, oversedation, or nausea. The only significant side effect of ITM was increased itching requiring diphenhydramine (24.6% vs 7.0%; $P = 0.002$; Table 4).

Table 2. Medication details.

Medication	No ITM (n = 115)	ITM (n = 65)	P
Intraoperative medication			
Total intraoperative MME	54.23 ± 35.67	90.29 ± 22.93	**<0.001**
IV MME (excluding ITM)	54.23 ± 35.67	37.41 ± 19.92	**<0.001**
ITM	N/A	65 (100)	N/A
ITM, μg	N/A	214.84 ± 35.27	N/A
ITM MME	N/A	53.71 ± 8.82	N/A
Fentanyl	107 (93.0)	60 (92.3)	1
Fentanyl, μg	191.36 ± 130.14	132.50 ± 63.50	**<0.001**
Morphine	1 (0.9)	17 (26.2)	**<0.001**
Morphine, mg	2.00 ± 0	5.83 ± 2.73	**<0.001**
Hydromorphone	83 (72.2)	20 (30.8)	**<0.001**
Hydromorphone, mg	1.32 ± 0.85	0.91 ± 0.61	**0.015**
Fluid received, mL	2547.2 ± 1415.8	2349.2 ± 1107.5	0.302
Postoperative medication			
Total PACU MME	21.83 ± 21.07	9.7 ± 31.23	**0.006**
Total floor MME	110.24 ± 139.92	88.0 ± 84.51	0.186
Total floor + PACU MME	132.07 ± 144.18	97.73 ± 91.04	0.052
Postoperative day 0 floor MME	13.64 ± 15.63	8.86 ± 13.55	**0.033**
Postoperative day 0 floor + PACU MME	35.47 ± 28.51	18.60 ± 35.47	**0.001**
Postoperative day 1 floor MME	35.19 ± 30.88	33.05 ± 28.33	0.638
Postoperative day 2 floor MME	21.41 ± 34.74	23.89 ± 27.54	0.599

Abbreviations: ITM, intrathecal morphine; IV, intravenous; ML, milliliter; MME, milligram morphine equivalent; PACU, postanesthesia care unit.
Note: P values < 0.05 in bold. Data are expressed as mean ± SD or *n* (%).

Table 4. Adverse events.

Adverse Event	No ITM (n = 115)	ITM (n = 65)	P
Urinary retention	11 (9.6)	9 (13.8)	0.528
Respiratory depression	33 (28.7)	21 (32.3)	0.715
Oversedation	1 (0.9)	3 (4.6)	0.267
Itching	8 (7.0)	16 (24.6)	**0.002**
Nausea	44 (38.3)	28 (43.1)	0.635

Abbreviation: ITM, intrathecal morphine.
Note: P values < 0.05 in bold. Data are expressed as mean ± SD or *n* (%).

There were no differences in LOS, hours or days, or percentage of patients who had a 0- or 1-day LOS between those who had ITM and those who did not. Additionally, there were no differences in discharge disposition, 90-day ED return, 90-day readmission, reason for ED return or readmission, 90-day complication, or complication type (Table 5).

DISCUSSION

In comparison to a matched cohort of 115 lumbar fusion patients not receiving ITM, those receiving low-dose ITM at the beginning of lumbar fusion received more intraoperative MME overall but less when excluding for the ITM dose. The overall increase in intraoperative MME administered to ITM patients in this study was likely due to the ITM dose itself. Postoperatively, ITM patients received less MME in PACU and on POD 0. Overall postoperative total narcotic consumption, however, was similar between groups. In a meta-analysis of 8 randomized controlled trials with 393 subjects who either received ITM or not, a significant decrease in the amount of morphine equivalent consumption was noted in the ITM group in the first 24 hours after surgery.[13] Similarly, in a prospective, randomized, double-blind placebocontrolled study of 68 spinal fusion patients, those who received ITM before wound closure required less initial narcotic delivery and utilized a PCA pump significantly less than those not receiving ITM.[14] A meta-analysis of 5 studies, including 3 randomized controlled trials and 2 retrospective medical record reviews of 636 pediatric patients undergoing spinal surgery with or without addition of ITM, revealed a significant delay in time to request for pain control and overall decrease in opiate consumption by POD 2 in the ITM group compared with the control group.[15] Finally, a prospective randomized controlled study of 90 patients with an ASA score of I or II undergoing lumbar laminectomy who received either pre-emptive ITM, postoperative ITM, or no ITM demonstrated a lower consumption of morphine in the pre-emptive and postoperative ITM groups compared with the control group, with the pre-emptive ITM group utilizing the least morphine in the first 24 hours.[16] The decrease in the total MME utilized by lumbar fusion patients receiving ITM in this study may be due to the administration of low-dose ITM at the onset of the case. While other similar studies have utilized ITM doses ranging from 0.25 to 0.5 mg ITM,[6,7] equivalent results appear to have been achieved with a notably lower dose, as shown here. Our results echo other studies in which the total amount of narcotics used within the first 24 hours after surgery is decreased in patients receiving ITM, demonstrating a benefit in the early postoperative period with potentially lower doses of ITM administered than previously reported.

When evaluating pain scores, ITM patients had lower overall pain scores in the PACU and on POD 0 and were less likely to have extreme pain (as denoted by a pain score >7) on POD 0 than patients who did not receive ITM. A retrospective study of 137 patients undergoing 1- or 2-level transforaminal interbody fusion who either did or did not receive intrathecal opioids revealed significantly lower postoperative pain scores in the intrathecal opioid group across the first 2 days of recovery compared with the control group.[17] In comparison, 44 patients in a case-control study comparing continuous subcutaneous morphine infusion alone and combined with ITM injection in posterior lumbar interbody fusion demonstrated lower visual analog scores in the ITM + subcutaneous group.[18] Our results support these conclusions from prior studies. The use of low-dose ITM injection at the onset of spinal surgery appears to

Table 5. Postoperative outcomes.

Outcome Measure	No ITM (n = 115)	ITM (n = 65)	P
Length of stay, h	96.77 ± 194.76	71.27 ± 45.08	0.182
Length of stay, d	3.70 ± 8.15	2.60 ± 1.88	0.170
0- or 1-d length of stay	50 (43.5)	20 (30.8)	0.128
Discharge home	99 (86.1)	61 (93.8)	0.179
90-d ED return	18 (15.7)	6 (9.2)	0.302
90-d readmission	19 (16.5)	10 (15.4)	0.989
90-d ED/readmission reason			0.889
DVT	1 (0.9)	1 (1.5)	
Medical	14 (12.2)	6 (9.2)	
Surgery related	3 (2.6)	1 (1.5)	
Surgery-related pain	9 (7.8)	5 (7.7)	
Wound infection	5 (4.3)	1 (1.5)	
90-d complication	14 (12.2)	7 (10.7)	0.952
90-d complication type			0.892
DVT	1 (0.9)	1 (1.5)	
Medical	4 (3.5)	3 (4.6)	
Revision surgery	3 (2.6)	1 (1.5)	
Surgery related	2 (1.7)	0 (0)	
Surgery-related pain	2 (1.7)	1 (1.5)	
Wound healing/infection	5 (4.3)	3 (4.6)	

Abbreviations: DVT, deep vein thrombosis; ED, emergency department; ITM, intrathecal morphine; OR, operating room.
Note: P values < 0.05 in bold. Data are expressed as mean ± SD or *n* (%).

decrease pain scores in the initial postoperative period, contributing to improved pain control overall after lumbar fusion.

The lower levels of pain reported and narcotics required on the day of surgery with ITM use reflect the benefits of pre-emptive analgesia in the lumbar fusion population. As a hydrophilic opioid, morphine results in broad-band analgesia with an extended duration of action when administered intrathecally.[19] By pre-emptively inhibiting nociceptive transmission, the reduction of central pain sensitization resulting from intraoperative incisional and inflammatory injury can be achieved at lower doses prior to the development of centralized hyperexcitability rather than after its establishment.[20] The significantly lower pain scores and MMEs required by ITM patients in the current study are in alignment with this theory. Furthermore, while we did not observe statistically significant differences in overall amounts of postoperative MMEs between groups ($P = 0.052$), patients receiving ITM did require 34.3 fewer MMEs, on average, during hospitalization, which may be of clinical significance. However, further study is needed to evaluate whether pre-emptive analgesia with ITM may reduce opioid requirements beyond the immediate postoperative period, as this finding is potentially confounded by LOS differences between groups.

In this study, ITM administration was not associated with increased rates of urinary retention, respiratory depression, or oversedation. In a prospective, randomized, double-blind, placebocontrolled study comparing ITM administration to no ITM administration in 46 patients undergoing posterior lumbar interbody fusion surgery, no differences in morphine-related side effects were noted between groups, and the ITM patients experienced only mild respiratory depression not requiring intervention in the first 4 hours postoperatively.[21] These findings are consistent with our results; however, there was an increased incidence of postoperative itching requiring diphenhydramine/nalbuphine hydrochloride administration in our ITM group. An analogous conclusion was made in a meta-analysis of 11 randomized controlled studies and 1 case-control study comparing ITM to a control group in spinal surgery which demonstrated increased risk of pruritis in the ITM group without increased risk of any other morphine-related complications.[22] Increased risk of pruritis may be due to greater overall MME utilization in the ITM group. A randomized double-blinded controlled trial comparing analgesia and side effects for low-dose ITM use in cesarian sections was performed; patients received either no ITM, 0.05, 0.1, or 0.2 mg ITM, and the incidence of pruritis increased in a dose-dependent manner.[23] This is consistent with the results of this study as the ITM group received more total MME during their procedure. Although pruritis and diphenhydramine administration are not completely benign, providers should consider the potential greater benefit to pain control and decreased opioid consumption achieved by ITM administration despite a comparatively minor inconvenience to the patient.

Finally, no differences in LOS, discharge disposition, 90-day ED returns, or 90-day readmissions were observed between groups. In a study of 32 patients enrolled in a randomized, double-blind control trial who received either ITM or a placebo, the ITM group did not experience a significantly different LOS or time to ambulation compared with those receiving a placebo.[24] This is consistent with our results, demonstrating that low-dose ITM use does not adversely affect outcomes in the first 90 days after surgery when compared with control groups. The lack of increased complications with ITM may contribute to decrease LOS in lumbar fusion patients and may decrease costs associated with longer stays or discharges to skilled nursing facilities. Further studies should be performed to determine whether pre-emptive ITM use combined with other analgesic medications has further benefits in these patients. A retrospective cohort study of 2 groups, one receiving ITM alone and the other receiving ITM + bupivacaine, demonstrated decreased LOS and perceived patient pain levels in the ITM + bupivacaine group.[25] While our results did not demonstrate significant differences in LOS in lumbar fusion patients, the opportunity for optimal intraoperative pain control regimens exists, which may decrease LOS overall. Given the efficacy of MMA administration in spinal surgery, the potential for new protocols that include ITM and other adjunct anesthetics should be explored to minimize pain and improve outcomes among lumbar fusion patients.

There are limitations to this study. As a retrospective medical record review performed at a single institution, the sample size is limited, and the results may not be as applicable to all institutions or patient populations. A detailed medical record review was performed to identify and exclude any confounding factors among the data, but confounders may still exist that this study was not powered to eliminate. Expansion of this study to a larger cohort over multiple institutions may eliminate confounding factors that were not eliminated within this study. A standard protocol for MMA including ITM

administration with evaluation over a longer period may also serve to further support the results outlined in this study.

CONCLUSION

ITM appears to be safe and effective for reducing early pain and narcotic consumption on the day of surgery for lumbar fusion patients. This study demonstrates similar results to prior studies but with lower doses of ITM administered to patients. It may hold value for incorporation into rapid recovery protocols as procedures continue to shift toward the ambulatory environment. However, further studies are needed to further delineate the benefits of ITM and determine protocols for dosing and utilization in lumbar fusion surgery.

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