

## Safety and Efficacy of Intrathecal Morphine for Lumbar Spine Surgery Using Two Different Doses: A Randomised Controlled Study

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### Abstract

**Context:** Several studies addressing Intrathecal Morphine (ITM) use following spine surgery have been published using low to high-dose of ITM. But the optimal dose of ITM with maximal analgesic property and minimal complication and side effects is yet to be decided. **Aims:** We aimed to compare the analgesic efficacy of two low doses of ITM, 0.3 mg and 0.4 mg in patients undergoing lumbar spine decompression, with or without instrumentation surgery. **Materials and Methods:** Fifty patients were enrolled in a double-blinded randomised controlled trial, and received either 0.3 mg or 0.4 mg of ITM. Post-operatively, all patients were given a Patient Controlled Analgesia (PCA) pump and observed for the first 24h in a step-down unit. Measurement of: Total fentanyl used during intra-operative period; Total PCA morphine consumed in first 24h; Intensity of pain; Sedation score; nausea; Vomiting; Pruritus; and occurrence of respiratory depression were recorded. **Statistical Analysis Used:** Statistical analysis was performed using Graph Pad Prism 6.0, La Jolla, CA, USA. Statistical significance of categorical variables between the groups was compared by Chi-square test and that of quantitative variables were compared using Student's *t*-test. **Results:** The total intra-operative fentanyl consumption and total PCA morphine use and the overall pain score over the first 24 h in the post-operative period was significantly low in 0.4 ITM Group. There was no difference in terms of sedation, nausea, vomiting and pruritus. There was no case of respiratory depression in either Group. **Conclusions:** 0.4 mg ITM provided superior analgesia in the post-operative period compared to 0.3 mg with no significant increase in the incidence of side effects.

**Keywords:** Intrathecal morphine; Lumbar spine surgery; Respiratory depression.

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### Introduction

Routine pre-operative use of opioid for pain management and soft tissue dissection in posterior spine surgery leads to significant post-operative pain.<sup>1-3</sup> There is growing evidence that acute post-operative pain also influences the development of chronic pain through central or peripheral

sensitization of receptors. Intra- and post-operative opioid-sparing may be regarded as surrogates of the true efficacy of an analgesic. In this regard intrathecal opioids are a novel way of post-operative analgesia as they produce "segmental analgesia" resulting in localized nociception without sensory, motor, autonomic, or systemic side effects.<sup>4</sup> They not only allow post-operative neurological

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assessment in immediate post-operative period but also avoid risk of orthostatic hypotension or motor in co-ordination that local anesthetics cause.<sup>5</sup> Due to its long duration of action, morphine is considered a better option for intrathecal administration. Previous studies have used 0.2–2.0 mg of Intrathecal Morphine (ITM) for post-operative pain control after lumbar spine surgery.<sup>1,6–9</sup> Studies have shown that low dose of ITM (<5  $\mu\text{g}/\text{kg}$ ) is safe and the incidence of side effects increases when ITM higher than 0.4 mg is used.<sup>10,11</sup>

This double-blind, randomized study was primarily designed to assess the post-operative analgesic effect of low doses ITM, i.e., 0.3 mg and 0.4 mg in adult patients undergoing posterior lumbar spine surgery. Cumulative Patient Controlled Analgesia (PCA) morphine consumption and post-operative pain scores were main outcome considered. Side effects and complications of ITM were also examined.

## Materials and Methods

This prospective, randomized, double blinded, comparative study was carried out after approval from the Institutional Ethics Committee of our hospital and written informed consent was obtained from eligible 50 patients. Patients of American Society of Anesthesiologists (ASA) Grade I and II, aged 18–70 years of either sex, undergoing elective lumbar laminectomy with or without fusion, and with or without instrumentation, and were considered for entry into the study. Exclusion criteria were pregnancy, allergy/intolerance to any of the study medications, chronic morphine use, history of sleep apnoea and inability to use patient PCA.

A computer generated block randomization scheme was used to stratify participants into 1 of 2 treatment regimens: ITM 0.3 mg (Group A) or ITM 0.4 mg (Group B). Primary investigators, patients, anesthesia providers and post-operative medical staff were blinded to treatment assignment.

Routine preparation of the patients was carried out as per our institutional standards for all patients undergoing lumbar spine surgery. Standard monitors were attached and patients were placed in sitting position, and the spinal puncture was performed at L3-L4 or L4-L5 interspace using a 25-gauge Quincke spinal needle.

Once free flow of cerebrospinal fluid had been recognized, the ITM (0.3 mg or 0.4 mg) in 2 ml normal saline 0.9% was injected. Patients received

standardized monitoring and an anesthetic regimen consisting of intravenous fentanyl 2–3  $\mu\text{g}/\text{kg}$  and thiopentone sodium 4–5  $\text{mg}/\text{kg}$ , with vecuronium 0.1  $\text{mg}/\text{kg}$  to facilitate endotracheal intubation. Anesthesia was maintained with oxygen, air, and sevoflurane (approximately 1 MAC).

Intra-operatively, all patient received ondansetron 0.15  $\text{mg}/\text{kg}$  (maximum dose of 8 mg) I.V. towards end of surgery for Post-operative Nausea and Vomiting (PONV) prophylaxis. A 20% increase in heart rate and/or arterial blood pressure from the pre-operative baseline was treated with fentanyl boluses of 25  $\mu\text{g}$  at 2.5-minute intervals until vital signs returned to baseline.<sup>12</sup> At the end of the surgery, sevoflurane was turned off and the neuromuscular blockade was reversed with neostigmine (50  $\mu\text{g}/\text{kg}$ ) and glycopyrrolate (10  $\mu\text{g}/\text{kg}$ ).

Post-operatively, all patients were given a PCA pump with initial programming consisting of morphine 1.0  $\text{mg}/\text{ml}$ , bolus of 0.02  $\text{mg}/\text{kg}$  (maximum 2.0 mg) and lockout of 5 min, with no background infusion. They also received I.V. paracetamol 1 gm every 6h for 24h post-operatively. Subsequent management of the PCA pump was at the discretion of the acute pain management anesthesiologist, who was blinded to patient allocations. PONV and pruritus was managed with additional dose of I.V. ondansetron 0.15  $\text{mg}/\text{kg}$  and /or dexamethasone 8 mg.

Patients were monitored for the first 24h post-operatively in a high dependency unit with standard monitoring facility including continuous oxygen saturation monitoring. The post-operative outcome measures that were evaluated and recorded were: Pain intensity, graded by 11 point Numeric Rating Scale (NRS) from 1 to 10; total PCA morphine used in the first 24 h post-operatively, measured in milligrams; degree of sedation, measured by Ramsey sedation score; if awake, 1-anxious, agitated, restless, 2-co-operative, oriented, tranquil, and 3-responsive to commands only; if asleep-4-brisk response to light glabellar tap or loud auditory stimulus, 5-sluggish response to light glabellar tap or loud auditory stimulus, and 6-no response to light glabellar tap or loud auditory stimulus. Side effects, such as nausea, vomiting, sedation, pruritus and episodes of respiratory depression (defined as respiratory rate < 9 breaths/min, room air oxygen saturation < 90% or need for naloxone to maintain an adequate tidal volume) were also recorded.

The sample size calculation was based on estimating a 30% decreased in post-operative morphine requirement as observed in the previous

studies.<sup>11,13,14</sup> A calculated sample size of 20 patients would be required to attain the power of at least 80% and 5% significance level with 90% confidence interval. Therefore, we enrolled 25 patients in each group.

Statistical analysis was performed using Graph Pad Prism 6.0, La Jolla, CA, USA. Statistical significance of categorical variables between the groups was compared by Chi-square test and that of quantitative variables were compared using Student's *t*-test. Ordinal variables were analysed using non-parametric based factorial ANOVA. Quantitative variables were presented as mean ± SD (standard deviation). *p* < 0.05 was considered statistically significant.

### Results

The groups were not significantly different according to patient age, sex, weight and American Society of Anesthesiologists classification, shown in **Table 1**. Total fentanyl used during the intra-operative period was significantly higher in Group A ( $150 \pm 25 \mu\text{gm}$  versus  $125 \pm 25 \mu\text{gm}$ ; *p* = 0.01) but there was no difference between the two Groups regarding, duration of surgery and whether a fusion was performed in addition to the lumbar decompression, shown in **Table 2**.

**Table 1:** Demographic characteristics of participants

Characteristics	Group A (0.3 mg of ITM)	Group B (0.4 mg of ITM)	<i>p</i> *
Age (years) as mean ± SD	53.1 ± 11.7	57.3 ± 12.9	0.23
Gender (female/male)	10/15	8/17	0.55
Weight (kg) as mean ± SD	64.8 ± 15.2	66.6 ± 12.8	0.65
ASA grade (I/II)	6/19	9/16	0.35

\*Calculated using Chi-square test or Student's *t*-test as appropriate, ITM: Intrathecal morphine

ASA: American Society of Anesthesiologists, SD: Standard Deviation.

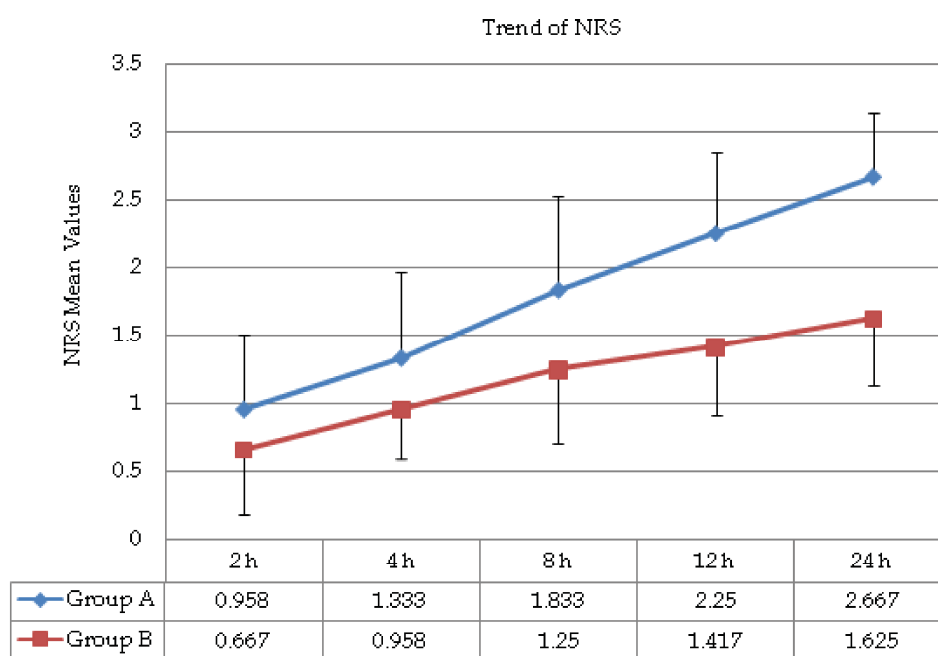
**Table 2:** Intra-operative data

Variables	Group A (0.3 mg of ITM)	Group B (0.4 mg of ITM)	<i>p</i> *
Duration of surgery (min) as mean ± SD	202 ± 15	195 ± 20	0.16
Total fentanyl consumption ( $\mu\text{gm}$ ) as mean ± SD	150 ± 25	125 ± 25	0.01
Fusion, n	11	9	0.35

\*Calculated using Chi-square test or Student's *t*-test as appropriate, ITM: Intrathecal Morphine:

SD: Standard Deviation.

The post-operative pain scores of were significantly lower in Group B at all points of time over first post-operative 24 h (*p* < 0.001). None of the patients in Group B had a pain score > 2 during this time period, displays in **Fig. 1**.



**Fig. 1:** Trend of change of NRS over time points between the two Groups, Group A: 0.3 mg intrathecal morphine, Group B: 0.4 mg intrathecal morphine, NRS: Numeric rating scale. Error bars represent standard deviations.

The average total PCA use over the first post-operative 24h was significantly less in Group B ( $5.5 \pm 1.72$  mg versus  $10.5 \pm 2.38$  mg;  $p = 0.001$ ), shown in **Table 3**. The mean sedation score was comparable between the two Groups at all points of times over the 24h post-operative period and none of the patients had score  $< 2$  or  $> 4$  at any occasion. The number of patients, complaining of nausea, vomiting and pruritus in the post-operative period was comparable between the two Groups and there were no episodes of respiratory depression experienced by patients in either Group, shown in **Table 3**.

**Table 3:** Post-operative data

Variables	Group A (0.3 mg of ITM)	Group B (0.4 mg of ITM)	$p^*$
Total 24 h PCA, morphine consumption, mg, as mean $\pm$ SD	$10.5 \pm 2.38$	$5.5 \pm 1.72$	0.001
Nausea, $n$	5	6	0.73
Vomiting, $n$	2	1	0.55
Pruritus, $n$	6	9	0.35
SpO <sub>2</sub> $< 90\%$	Nil	Nil	
RR $< 9/min$	Nil	Nil	
Sedation score of $< 2$ or $> 4$	Nil	Nil	
Bradycardia (HR $< 50/min$ )	Nil	Nil	

\*Calculated using Chi-square test or Student's  $t$ -test as appropriate, ITM: Intrathecal Morphine, SD: Standard Deviation, PCA: Patient Controlled Anesthesia, SpO<sub>2</sub>: Oxygen saturation in room air; RR: Respiratory Rate; HR: Heart Rate

## Discussion

Patient undergoing lumbar spine surgery can experience severe post-operative pain which may potentially prolong recovery, and increase post-operative morbidity and complications.<sup>15</sup> This pain is most severe during the first 12h after even at rest and it increases considerably with movement due to the reflex spasm of paraspinal muscles that is triggered by the primary wound pain. On movement, pain remains severe for 48h and produces discomfort that can interfere with patient mobilization, increasing the length of stay in the hospital.<sup>16,17</sup>

It has been shown in previous studies that the degree of the induced respiratory depression was related to the dose of ITM. High doses of ITM (0.8–2 mg) was associated with increased incidence of late respiratory depression. However, patients receiving lower doses of ITM (0.3–0.4 mg) the risk of respiratory depression was minimal.<sup>18</sup> The practice guidelines by ASA Task Force for the

administration of neuraxial opioids also advocates the lowest efficacious dose of neuraxial opioid to minimize the risk of respiratory depression.<sup>19</sup> The present study has used the same approach of low dose ITM to prevent respiratory depression. Single shot ITM provides long-lasting analgesia and has many advantages over epidural catheter or I.V. PCA. Technically, the intrathecal injection is a simple technique compared to epidural catheter placement and does not need additional equipment as required in epidural catheter or I.V. PCA.<sup>20,21</sup>

Meylan *et al.* did a meta-analysis of 27 studies where patients undergoing major surgeries, received ITM dose between 0.1 to 4 mg without local anesthetics. They observed that pain intensity was significantly decreased over the first post-operative 24 h in the ITM Group, but were unable to determine the optimal dose of ITM (*i.e.*, the dose that has adequate analgesic efficacy with minimal complications and side effects).<sup>22</sup> In our study, ITM dose of 0.4 mg produced superior analgesia not only in the post-operative period but also the intra-operative dose requirement of fentanyl was significantly reduced when compared with 0.3 mg ITM. There was no incidence of respiratory depression and the side effects were comparable. Therefore, 0.4 mg of ITM can be considered as the optimal dose in patients undergoing lumbar spine surgeries.

Fares *et al.* compared 0.2, 0.5, and 1 mg ITM and noticed that 1 mg morphine provided superior analgesia for 48h post-operative but the incidence of respiratory depression was also high compared to 0.2 mg. They opined that in order to minimize the incidence of post-operative respiratory depression the ITM dose should be restricted to 0.5 mg.<sup>23</sup> In our study, low dose of ITM (0.3 mg and 0.4 mg) was used in both the groups and none of the patient had any episode of post-operative respiratory depression and the quality of analgesia was significantly better in 0.4 mg Group.

Prior study have shown that, as long as ITM is used in low doses ( $< 5 \mu\text{g}/\text{kg}$ ), increasing the ITM dose will reduce the systemic opioid consumption thus minimizing the side effects associated with parenteral narcotics.<sup>1</sup> Similar results were also observed in our study, as we increased the dose of ITM from 0.3 to 0.4 mg, there was a significant decrease in morphine consumption over 24h without any significant increase in side effects. The difference was found to be statistically significant ( $p = 0.001$ ).

ITM dose of 0.4 mg has been used previously for post-operative pain control after posterior lumbar



body fusion surgery. In this study, the author demonstrated the efficacy of 0.4 mg ITM as indicated by a significantly lower cumulative piritramide requirement without any serious increase of opioid related side effects.<sup>2</sup> Compared to above mentioned study we did not use a placebo but managed to demonstrate a superior analgesic profile of 0.4 mg of ITM, compared to 0.3 mg ITM.

Preincisional ITM has been shown to prevent central sensitization and thus prevent chronic pain.<sup>24</sup> Compared to other studies where ITM was used during the intra-operative period, we used preincisional ITM which resulted in significantly less total fentanyl use in Group B during the intra-operative period. There were no episodes of respiratory depression in either Group. The incidence of nausea, vomiting, and pruritus was comparable in both the Groups. None of the patient in either Group had a sedation score of < 2 or > 4 during the 24h, post-operative period.

This study has certain limitations such as inter-patient pain threshold variability, which was not considered. However, no patient was on any long acting analgesic preparation. Since all the patients were managed with I.V. PCA in the post-operative period, it was difficult to determine the time to first analgesic dose requirement as patients often ended up demanding the dose of analgesic based on their own pain threshold. Hence, the duration of post-operative analgesia could not be reliably predicted for the two Groups. As the sample size was small, a larger study would be required to confirm the results.

## Conclusion

Patients undergoing lumbar laminectomy, with or without fusion, under general anesthesia and receiving systemic opioids for break-through pain after operation, the additional use of ITM decreases pain intensity after surgery. Serious side effect such as respiratory depression could be minimized by using appropriate dose of ITM, and other side effects such as nausea, vomiting, and pruritus can be easily managed by injection of ondansetron and dexamethasone. The present study found that single dose of 0.4 mg ITM provided superior analgesia without any increase in the side effects as compared to 0.3 mg ITM. Further studies, including larger sample sizes, are required to show that 0.4 mg ITM as highly efficient analgesic technique with minimal side effects after lumbar spine decompression and instrumentation surgery.

## Key Messages

Intense post-operative pain following lumbar spine surgery can be easily managed with appropriate preincisional low dose of ITM. 0.4 mg of ITM can be considered as the optimal intrathecal dose as it provides superior analgesic profile during intra and post-operative period with minimal side effects.

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