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Research Article

Intramuscular Methadone vs. Morphine for Postoperative Pain after Lumbar Disc Surgery: A Double-Blind Randomized Trial

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ABSTRACT

Background: Postoperative pain remains one of the most prevalent clinical challenges and, despite advances in anesthesia and analgesia, is not yet fully measurable or optimally controlled. Although morphine is among the most commonly used opioids for postoperative pain management, its adverse effect profile imposes limitations on its clinical utility. Methadone, a long-acting opioid with multiple mechanisms of action, may represent a suitable alternative for improving postoperative analgesic quality. However, evidence comparing intramuscular methadone with intramuscular morphine in spinal surgeries is limited. This study aimed to compare the effects of intramuscular methadone and morphine on pain intensity, opioid requirements, recovery time, and postoperative adverse effects following lumbar disc surgery.

Methods: This double-blind randomized clinical trial was conducted on 80 patients scheduled for lumbar disc surgery with American Society of Anesthesiologists (ASA) physical status I–II. Patients were randomly assigned into two equal groups to receive either intramuscular methadone (0.1 mg/kg) or intramuscular morphine (0.1 mg/kg), administered 30 minutes prior to the end of surgery. Pain intensity was assessed using the Visual Analog Scale (VAS) at 4, 8, 12, and 24 hours after extubation. Additionally, rescue morphine consumption, time to achieve an Aldrete score >9, hemodynamic parameters, and the incidence of adverse effects were compared between the groups. Data were analyzed using SPSS software with appropriate statistical tests.

Results: Mean pain scores at all measured time points were significantly lower in the methadone group compared to the morphine group ($p < 0.001$). Rescue morphine consumption within the first 24 hours postoperatively was also significantly lower in the methadone group ($p < 0.001$). Patients receiving methadone achieved an Aldrete score >9 in a shorter time and demonstrated greater hemodynamic stability. The incidence of hypotension and bradycardia was higher in the morphine group, whereas no significant difference was observed between the groups regarding nausea and vomiting.

Conclusion: The findings indicate that intramuscular methadone provides more effective postoperative pain control than intramuscular morphine following lumbar disc surgery. It is associated with reduced need for rescue opioids, improved recovery indices, and a lower incidence of certain adverse effects. Methadone may therefore be considered a safe and effective option in postoperative pain management protocols for spinal surgeries.

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Introduction

Postoperative pain remains one of the most common clinical challenges, and, despite advances in anesthesia and analgesic techniques, it is not yet fully measurable or optimally controlled [1]. Its intensity and characteristics are influenced by multiple factors, including the type of surgery, the extent of tissue trauma, patient-specific conditions, and the analgesic strategy employed. Evidence indicates that a substantial proportion of patients experience moderate to severe pain within the first 72 hours after surgery, which can adversely affect recovery. Inadequate pain control is associated with numerous complications, including increased surgical stress response, cardiovascular events, thromboembolism, impaired mobility, chronic pain development, patient dissatisfaction, and even increased mortality [2]. Therefore, the selection of an effective analgesic strategy is critical, particularly in major surgical procedures. Lumbar disc surgery is frequently associated with significant postoperative pain. These patients often present with chronic neuropathic pain and opioid tolerance, which complicate effective pain management.

Current strategies for postoperative pain management include patient-controlled analgesia (PCA), neuraxial techniques such as spinal and epidural analgesia, ketamine infusion, gabapentinoids, acetaminophen, and nonsteroidal anti-inflammatory drugs (NSAIDs). Although these approaches are commonly used, each is associated with specific limitations related to efficacy, feasibility, or adverse effects [5–7]. Morphine continues to be among the most frequently administered opioids for postoperative analgesia; however, its clinical use may be limited by pharmacokinetic characteristics and well-recognized side effects, including nausea, pruritus, urinary retention, and respiratory depression [8–10].

Methadone is a synthetic opioid with a prolonged duration of action that exerts analgesic effects primarily through μ-opioid receptor activation while also functioning as an N-methyl-D-aspartate (NMDA) receptor antagonist. In addition, inhibition of serotonin and norepinephrine reuptake may contribute to its central analgesic properties and enhanced modulation of nociceptive pathways [7–8]. These pharmacologic features have generated interest in methadone as an alternative perioperative analgesic agent. Previous investigations have reported that intravenous methadone may reduce postoperative opioid consumption in patients undergoing major surgical procedures [4–6]. Nevertheless, access to intravenous methadone remains limited in some healthcare settings, including Iran, and evidence regarding the efficacy of intramuscular administration remains scarce. Considering the high surgical burden of lumbar disc procedures, the complexity of postoperative pain control in this population, and the potential advantages of methadone's pharmacologic profile, further evaluation of intramuscular methadone compared with morphine is justified. Therefore, the present study aimed to compare these two agents with respect to postoperative pain intensity, supplemental opioid requirements, recovery characteristics, and treatment-related adverse events.

To date, limited evidence exists regarding this comparison in spinal surgeries. This study aims to address this gap and provide evidence applicable to settings where intravenous methadone is unavailable.

Methods

This study was a parallel-group, double-blind randomized controlled trial designed to compare the efficacy and safety of intramuscular methadone (0.1 mg/kg) versus intramuscular morphine (0.1 mg/kg) for postoperative pain control following lumbar disc surgery. Eligible participants were adults aged 18–70 years undergoing elective lumbar disc surgery with American Society of Anesthesiologists (ASA) physical statuses I or II. Exclusion criteria included a history of substance use disorder, chronic systemic disease, pre-existing radicular pain, psychiatric disorders, seizure disorders, cognitive impairment, reduced level of consciousness, or hemodynamic instability. Participants were randomly assigned in a 1:1 ratio to receive either intramuscular methadone or intramuscular morphine. Randomization was performed using a computer-generated block randomization sequence with variable block sizes of 4 and 6, prepared by an independent statistician. Allocation concealment was ensured באמצעות sequentially numbered, sealed, opaque envelopes. Blinding was maintained by preparing study medications in identical syringes with respect to volume, color, and appearance by a staff member not involved in patient care or outcome assessment. Participants, anesthesiologists, outcome assessors, and data analysts were all blinded to group allocation until completion of the analysis. The sample size was calculated to detect a clinically meaningful difference in postoperative pain scores, assuming a standard deviation of 2.5, an effect size of 1.1, a two-sided significance level of 0.05, and a statistical power of 80%. Based on these assumptions, 80 participants (40 per group) were required. All participants received a standardized general anesthesia protocol consisting of premedication with midazolam (0.02 mg/kg) and fentanyl (2 μg/kg), induction with thiopental (3–5 mg/kg) and cisatracurium (0.15 mg/kg), and maintenance with isoflurane in combination with intermittent fentanyl (1–2 μg/kg every 45–60 minutes). The study drug was administered intramuscularly 30 minutes before the end of surgery, defined as 20 minutes after the last fentanyl

dose. The primary outcome was postoperative pain intensity, measured using the Visual Analog Scale (VAS; range 0–10) at 4, 8, 12, and 24 hours after extubation. Secondary outcomes included total rescue opioid consumption in the first 24 hours postoperatively, time from extubation to achieving an Aldrete score greater than 9 (defined as readiness for discharge from the post-anesthesia care unit), time from positioning to extubation, and the incidence of adverse events. Rescue analgesia was provided with intravenous morphine (3 mg) when VAS exceeded 4, with repeat dosing as required; rectal diclofenac was administered if additional analgesia was needed. Hemodynamic parameters were monitored continuously using noninvasive blood pressure measurement, electrocardiography, and pulse oximetry. Statistical analysis was performed using SPSS version 27. Continuous variables were reported as mean ± standard deviation and compared using the independent-samples t-test. Categorical variables were presented as frequencies and percentages and analyzed using the chi-square test. For non-normally distributed data, the Mann–Whitney U test was used. All analyses were conducted on a two-sided basis, and a P value of less than 0.05 was considered statistically significant.

Results

A total of 80 eligible patients were enrolled in the study and randomly assigned in equal numbers to receive intramuscular methadone or intramuscular morphine, with 40 patients in each group. Baseline demographic characteristics showed no statistically significant difference in age between the two groups. The mean age was 42.23 ± 9.59 years in the methadone group and 44.25 ± 9.66 years in the morphine group ($p = 0.35$), indicating comparability between groups with respect to age and minimizing its potential confounding effect. However, the distribution of sex differed between the groups. In the methadone group, the majority of patients were female, comprising 97.5% of participants, while only 2.5% were male. In contrast, the morphine group demonstrated a more balanced sex distribution, with 52.5% male and 47.5% female participants. Although this imbalance was observed despite randomization, it was considered a potential limitation and taken into account in the interpretation of the findings, particularly given that the primary analyses focused on clinical outcomes such as pain intensity, opioid consumption, hemodynamic parameters, and recovery time. Assessment of hemodynamic parameters during the recovery period revealed that the mean heart rate was significantly lower in the methadone group compared to the morphine group. The mean heart rate was 72.73 ± 5.36 beats per minute in the methadone group and 79.07 ± 6.28 beats per minute in the morphine group ($p < 0.001$). This difference was not only statistically significant but also clinically meaningful, as supported by the calculated effect size. Similarly, mean arterial pressure (MAP) was significantly lower in the methadone group. The mean MAP was 85.00 ± 5.47 mmHg in the methadone group compared to 89.51 ± 5.26 mmHg in the morphine group ($p < 0.001$). These findings indicate greater hemodynamic stability in patients receiving methadone compared with those receiving morphine (Table 1).

Based on the data presented in (Table 1), comparison of time-related indices between the methadone and morphine groups demonstrated notable differences in postoperative recovery and patient management during the post-anesthesia period. The mean time from change in patient positioning to extubation was shorter in the methadone group (37.00 ± 4.42 minutes) compared to the morphine group (40.31 ± 4.81 minutes). This finding suggests that patients receiving methadone achieved readiness for extubation more rapidly following repositioning, which may reflect faster recovery of consciousness and more stable respiratory function. Postoperative pain intensity was assessed at predefined time points using the Visual Analog Scale (VAS), and longitudinal changes were analyzed using a repeated-measures model. Pain intensity decreased significantly over time in both groups ($p < 0.001$), consistent with the expected postoperative course. Pain levels were highest in the early postoperative period, peaking at approximately 2 hours, and progressively declined to the lowest levels at 24 hours after surgery, indicating an overall downward trend. Importantly, the main effect of the treatment group was statistically significant, with the methadone group demonstrating consistently lower mean VAS scores compared to the morphine group (Table 2). This indicates that patients receiving methadone experienced less pain across all measured time points.

However, the interaction between time and treatment group was not statistically significant, suggesting that although the trajectory of pain reduction over time was similar in both groups, the overall pain intensity remained lower in the methadone group throughout the follow-up period. Comparative analysis of rescue opioid consumption during the first 24 hours postoperatively showed that patients in the methadone group required significantly lower doses of morphine than those in the morphine group. The mean morphine consumption was 6.05 ± 2.24 mg in the methadone group and 10.93 ± 2.52 mg in the morphine group ($p < 0.001$). The large effect size associated with this difference underscores its clinical relevance and indicates that intramuscular methadone substantially reduced the need for additional opioid administration (Table 1). Evaluation of adverse events revealed no statistically significant difference between the two groups in the incidence of postoperative nausea and vomiting. However, bradycardia and hypotension occurred more frequently in the morphine group compared to the methadone group. Notably, a

reduction in blood pressure exceeding 20% from baseline was more prevalent among patients receiving morphine, which may be clinically significant. These findings suggest that methadone, in comparison with morphine, is associated with a more favorable safety profile in patients undergoing lumbar disc surgery (Table 2,3). Furthermore, based on the test of within-subjects effects (time × group), the interaction between time and treatment group was not statistically significant. This finding indicates that the pattern of change in pain intensity over time did not differ significantly between the two groups. In other words, both groups exhibited a similar trajectory of pain reduction over time, despite the overall lower pain scores observed in the methadone group (Table 4).

Table 1- Comparison of continuous variables between methadone and morphine groups

Variable	Group	N	Mean	SD	SEM*
Age (years)	Methadone	40	42.23	9.60	1.52
	Morphine	40	44.25	9.67	1.53
Heart Rate in Recovery (beats/min)	Methadone	40	72.73	5.36	0.85
	Morphine	40	79.07	6.28	0.99
Mean Arterial Pressure in Recovery (mmHg)	Methadone	40	85.00	5.47	0.86
	Morphine	40	89.50	5.26	0.83
Rescue Morphine Consumption (24 h, mg)	Methadone	40	6.05	2.24	0.36
	Morphine	40	10.90	2.50	0.40
Recovery Time (min)	Methadone	40	44.80	8.16	1.29
	Morphine	40	56.28	7.85	1.24
Time from Position Change to Extubation (min.)	Methadone	40	37.00	4.42	0.70
	Morphine	40	40.31	4.81	0.76
Time to Transfer to Recovery Unit (min.)	Methadone	40	9.96	3.04	0.48
	Morphine	40	14.76	2.80	0.44

*Standard error of the mean.

Table 2- Incidence of hypotension in patients receiving methadone versus morphine

Group	Without hypotension n (%)	With hypotension n (%)	Total (n)
Methadone	38 (95.0)	2 (5.0)	40
Morphine	26 (65.0)	14 (35.0)	40

Table 3- Incidence of bradycardia in patients receiving methadone versus morphine

Group	Without bradycardia n (%)	With bradycardia n (%)	Total (n)
Methadone	39 (97.5)	1 (2.5)	40
Morphine	31 (77.5)	9 (22.5)	40

Table 4- Interaction effect of time and treatment group on pain intensity (VAS scores)

Group	Time Point	Mean VAS Score	95% CI (Lower)	95% CI (Upper)
Methadone	1	4.68	4.41	4.94
	2	4.25	3.99	4.51
	3	3.38	3.05	3.70
	4	2.90	2.54	3.26
Morphine	1	5.60	5.34	5.86
	2	5.03	4.77	5.28
	3	4.23	3.90	4.55
	4	3.98	3.61	4.34

Overall, the findings of this study demonstrate that intramuscular methadone, compared with intramuscular morphine, resulted in superior postoperative pain control, reduced requirement for rescue opioids, greater hemodynamic stability, and faster recovery. In addition, methadone was associated with a lower incidence of adverse effects. These differences were statistically significant ($p < 0.01$). Moreover, the observed effect size (partial eta squared ≈ 0.40) indicates that the magnitude of these differences is not only statistically significant but also clinically meaningful.

Discussion

The findings of this study clearly demonstrate that intramuscular administration of methadone (0.1 mg/kg, 30 minutes prior to the end of surgery) provides more effective postoperative pain control compared with

intramuscular morphine at an equivalent dose in patients undergoing lumbar disc surgery. Patients who received intramuscular methadone reported consistently lower postoperative pain scores than those in the morphine group at all assessed intervals (4, 8, 12, and 24 hours after extubation), and these differences remained statistically significant across the entire observation period ($p < 0.05$). This pattern suggests that methadone maintains its analgesic advantage even when administered intramuscularly and may provide a longer-lasting postoperative analgesic effect. Several pharmacologic characteristics of methadone may explain these findings, including its prolonged elimination half-life, high affinity for μ-opioid receptors, and additional activity as an N-methyl-D-aspartate (NMDA) receptor antagonist. NMDA receptor blockade has been associated with reduced central sensitization, attenuation of opioid tolerance, decreased opioid-induced hyperalgesia, and improved control of neuropathic pain mechanisms, which may be particularly important in patients undergoing spinal procedures [11–17]. Another notable finding of this study was the lower need for rescue analgesia among patients in the methadone group during the first postoperative day. Compared with patients who received morphine, these individuals required fewer supplemental doses of intravenous morphine (3 mg administered for VAS > 4). From a clinical perspective, this reduction is relevant because it reflects not only more effective primary pain control but also decreased exposure to additional short-acting opioids. Limiting cumulative opioid administration may reduce the likelihood of opioid-related adverse events such as postoperative nausea and vomiting, excessive sedation, urinary retention, and respiratory compromise. Similar opioid-sparing effects of methadone have been described in previous studies, especially in major surgical procedures and spine surgery, where postoperative pain is typically intense and extends beyond the immediate recovery period [18–21].

With respect to hemodynamic outcomes, patients treated with methadone demonstrated more stable postoperative profiles during recovery, characterized by lower heart rate and mean arterial pressure values and less fluctuation over time compared with the morphine group. A plausible explanation is that improved analgesia reduced sympathetic activation, as uncontrolled postoperative pain is known to contribute substantially to cardiovascular instability in the early postoperative phase [22]. The greater frequency of hypotension and bradycardia in the morphine group may further support the favorable safety profile of methadone, particularly in patients who are more vulnerable to perioperative cardiovascular fluctuations, including middle-aged and older adults. In addition to analgesic outcomes, patients receiving methadone demonstrated faster postoperative recovery. This was reflected by a shorter interval from positioning to extubation, earlier attainment of an Aldrete score above 9, and reduced length of stay in the recovery unit. These observations are consistent with Enhanced Recovery After Surgery (ERAS) concepts, which prioritize effective pain control, attenuation of surgical stress responses, and earlier functional recovery. From a practical standpoint, improved recovery efficiency may contribute to better utilization of recovery resources, reduced hospital burden, and improved patient experience [22–24]. The shorter interval from positioning to extubation observed in the methadone group may indicate earlier restoration of consciousness and more coordinated respiratory recovery after anesthesia. Such improvements could potentially decrease the need for postoperative respiratory support and reduce the likelihood of respiratory-related complications. Likewise, the shorter time required for transfer to the recovery unit may reflect greater perioperative stability and smoother emergence from anesthesia. The reduction in overall recovery duration is likely multifactorial and may be related to more effective analgesia, lower consumption of supplemental medications, and decreased occurrence of symptoms such as agitation or postoperative discomfort [15,19]. With regard to postoperative adverse events, the incidence of nausea and vomiting did not differ significantly between groups. In contrast, episodes of hypotension and bradycardia occurred more frequently among patients receiving morphine, emphasizing that analgesic efficacy should be interpreted alongside safety considerations. Pruritus showed one of the most pronounced between-group differences, occurring substantially less often in the methadone group (5% versus 50%). This finding may be associated with differences in pharmacologic characteristics between the two agents, including histamine release profiles, receptor interactions, and overall opioid-related side-effect mechanisms [20–25]. Lower rates of pruritus may improve postoperative comfort, reduce the need for additional treatment, and simplify postoperative monitoring, ultimately improving treatment tolerability. One of the strengths of the present study is that it evaluates intramuscular methadone in a setting that closely reflects routine clinical practice, particularly in regions where intravenous methadone is not consistently accessible, including Iran. This increases the practical relevance of the findings and contributes evidence in an area with limited available data. However, several limitations should be acknowledged. The sample size was relatively small, follow-up was limited to the early postoperative period, and the results were obtained from a specific surgical population, which may affect generalizability. Further studies involving larger cohorts, extended follow-up, and comparisons with multimodal analgesic approaches are needed to confirm these findings and better define the role of intramuscular methadone in perioperative pain management.

Conclusion

Based on the findings of this study, intramuscular methadone was associated with a significant reduction in postoperative pain intensity, decreased need for rescue opioid consumption, improved hemodynamic stability, faster recovery, and a lower incidence of certain adverse effects compared with intramuscular morphine in patients undergoing lumbar disc surgery. These results suggest that methadone may be considered an effective and safe alternative for postoperative pain management in spinal surgeries.

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Ethics approval and consent to participate

The trial was conducted at Rouhani Hospital, Babol, Iran, after obtaining approval from the institutional ethics committee (IR.MUBABOL.HRI.REC.1403.285). Written informed consent was obtained from all participants prior to enrollment.

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