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Use of Intraoperative Ketamine and Methadone during Lumbar Spine Surgery: A Retrospective Study

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Abstract

Introduction: This retrospective chart review study was designed to assess the effect of administering intraoperative ketamine and methadone (vs. either drug alone) on postoperative pain and opioid consumption in patients undergoing elective spine surgery.

Methods: After IRB approval, we reviewed 268 patient charts, aged 18-80 years undergoing elective lumbar spine surgery. They were assigned to one of three groups: (1) ketamine (n= 90), (2) methadone only (n= 90), (3) and ketamine + methadone (n=88). The data collected included demographic information, medical history, pre-procedure medications, pre-operative pain scores and morphine equivalents, intra/postoperative-data, pain scores, opioid consumption, and medication dosages at 24, 48, and 72 hours postoperatively.

Results: Patients receiving a combination of ketamine + methadone reported a higher postoperative pain score ($p<0.0001$), greater usage of opioid ($p<0.0001$) and adjuvants analgesics ($p<0.05$) at 24, 48, and 72 hours after undergoing spine surgery compared to patients receiving ketamine or methadone alone for intraoperative analgesia. However, patients in the ketamine + methadone combination group had a greater chronic usage of opioid analgesic medication prior to this operation.

Conclusion: In this retrospective chart review, the combined use of ketamine and methadone did not result in an advantage with respect to reducing postoperative pain scores or analgesic usage compared to ketamine or methadone alone in patients undergoing lumbar spine surgery. These negative findings were likely related to differences among the study populations with respect to chronic usage of opioid medications.

Keywords: Ketamine; Methadone; Lumbar surgery; VRS pain score; Opioid requirements; PONV; Antiemetic consumption; Duration of hospital stay

Introduction

Post-lumbar spine surgery pain is associated with a high incidence of both pre-existing chronic pain conditions and chronic postsurgical pain, recurring back pain, disability, morbidity and postoperative complications [1]. Baseline opioid requirements in this group of patients are typically higher than the general population and the intra-operative and post-operative requirements could be increased along with the associated more frequent side effects and complications [2]. Many so-called co-analgesics or adjuvant

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drugs, such as anticonvulsants, antidepressants, nonsteroidal anti-inflammatory drugs (NSAIDs), NMDA (N-methyl-D-aspartate) receptor antagonists, and alpha-2-agonists may possess opiate-sparing effects, contributing to the management of perioperative pain by modifying nociceptive system changes resulting from tissue injury [3].

N-methyl-D-aspartate (NMDA) receptor antagonists such as ketamine and methadone have been shown to have opioid sparing effects, minimize opioid tolerance, and improve quality of postoperative pain control in chronic pain patients [4]. The side effects and pharmacology of these two drugs are well known [5,6]. Both ketamine and methadone individually exhibit analgesic properties, with the former having the benefit of maintaining respiratory function while the latter provides more prolonged analgesia.

The opioid-sparing effects and pain relief from ketamine have been well-documented. A 2021 meta-analysis showed that there were significant improvements in resting pain scores at 4, 12, and 24 hours post-operatively in ketamine patients compared to placebo [7]. In another meta-analysis of 37 trials (> 2000 patients) with perioperative ketamine usage, post-surgical opiate requirements were less than placebo in the first 24 to 48 hours. In post spine surgery patients, there was a 30% reduction in morphine consumption over the first 48 hours after surgery, and a 25% visual analog scale (VAS) pain score reduction in the post-anesthesia care unit [8]. Even at 6 weeks, postoperative pain scores and opiate consumption were significantly less in the ketamine group over the placebo group [8].

Patients given methadone during anesthetic induction demonstrated a 50% reduction in opiate requirements and VAS pain scores at 48hr post spine surgery [9]. Methadone showed to be superior to morphine in duration of postoperative pain relief and opioid requirements. In one study, the methadone group averaged 20.7 hours of sustained post-surgical pain relief compared to 6 hours with morphine and required significantly less quantities (11.5 + 8.5 mg vs. 41 + 14.1 mg) [9]. Similar studies have confirmed methadone's benefits [10,11]. These findings suggest Ketamine is effective for controlling postoperative pain and reducing opioid side effects for the first 24 hours, whereas methadone can provide pain relief for up to 48 hours.

Although both ketamine and methadone can provide significant postoperative pain relief, as well as opiate-sparing effects for patients suffering from chronic pain, their combined effects on postoperative pain remain largely unknown. This retrospective chart review aimed to study the effects of combining intraoperative ketamine and methadone on postoperative pain scores and opioid usage in patients undergoing lumbar spine surgery compared to simply administering ketamine or methadone alone for intraoperative analgesia.

Methods

This was a retrospective study approved by the Institutional Review Board of Cedars-Sinai Medical Center. A total of 268 patients' charts, all of whom underwent lumbar spine procedures between 2014 and 2022 at this institution and were administered intra-operative Ketamine and/or Methadone, were enrolled in this study. Initially, the investigator reviewed 550 medical records of subjects who underwent lumbar spine surgery, and intraoperatively were administered any of the drugs this study is specifically analyzing, and the data was collected and separated into three groups: ketamine alone, methadone alone, and a combo of ketamine + methadone. In the ketamine group, 90 patients received ketamine boluses and/or IV infusions intra-operatively in addition to opioids. In the methadone group, 90 patients received IV methadone intra-operatively in addition to opioids. In ketamine + methadone, 88 patients received IV ketamine boluses and/or infusions along with IV methadone boluses intra-operatively in addition to opioids.

The following data were collected and studied: age, gender, weight and BMI, race, ASA physical status, past medical and surgical history, social history (smoking), history of post-operative nausea and vomiting, current medications, pre-operative morphine equivalents, history of chronic pain, history of motion sickness, pre-operative pain baseline, and the number of spinal/lumbar levels involved. Intra-operative data collected includes duration of surgery (from skin incision to closure), duration of anesthesia (from IV induction until anesthetic drug discontinuation), dosages of medications given intra-operatively (e.g., anesthetics, analgesics, adjuncts, and rescue medications), and intra-operative morphine equivalents. Immediate post-operative findings in the Post-Anesthesia Care Unit (PACU) were also collected and studied, including: PACU length of stay [in minutes], initial post-operative VRS pain score, medication requirements (including opioids, other analgesics, muscle relaxants, antiemetics) as well as side effects and/or complications, and immediate post-operative morphine equivalents. Post-operatively, VRS pain scores, medication requirements (including opioids, other analgesics, muscle relaxants, antiemetics), morphine equivalents were measured and calculated at the 24-, 48-, and 72-hour post-operative periods.

Statistical analysis

The analysis was performed using SAS 9.3 for Windows (SAS Institute, Cary, NC, USA). Our dataset contained both categorical and continuous measurements. For categorical measures, we presented total numbers (n) and used Chi-square test (or Fisher's exact test) to conduct the group comparisons. For continuous measures, we presented mean values with their standard deviations and performed the one-

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way ANOVA and the Newman-Keuls multiple comparison test among those 4 groups as well as between each individual group when appropriate. All tests were two-sided and p-values ≤ 0.05 were considered to be statistically-significant.

Results

The three groups were comparable with respect to demographic and clinical characteristics including age, gender, BMI, race, ASA, smoking, history of PONV, average number of prior spine surgeries, duration of anesthesia, surgery and PACU recovery stay, medications taken prior to admission (except in morphine Equivalents mg higher in the combo group) among the three treatment groups (Table 1,2 and 3).

Discussion

Postoperative pain management is a vital part of an anesthesia providers' responsibility. Ketamine and methadone each possess analgesic properties, with ketamine specifically maintaining respiratory function and methadone offering extended opioid relief. Both medications also reduce the need for opioids following surgery. A study looking at anti-nociceptive synergy from the combination of opioid receptor agonists and NMDA receptor antagonists found synergy between NMDA antagonists and opioids specifically methadone to produce antinociception in experimental neuropathy [12]. In an experimental neuropathy study, researchers discovered that there is a synergistic effect between NMDA receptor antagonists and opioids, specifically

Table 1: Demographic characteristics and medications prior to admission among the three groups

	Ketamine (n = 90)	Methadone (n = 90)	Ketamine + Methadone (n = 88)	p-value
Age *(y)*	58 ± 12	61 ± 11	58 ± 11	0.187
Gender (Female/Male) *(n)*	43 / 47	46 / 44	49 / 39	0.57
BMI *(Kg/m²)*	27 ± 6	27 ± 6	29 ± 6	0.103
Race Asian/Black/White/Hispanic/Other *(n)*	3/3/81/2/1	8/2/76/2/2	0/1/85/1/1	0.35
ASA (I/II-III/IV) *(n)*	4/84/2	7/82/1	2/86/0	0.48
Smoker *(n)*	9	3	4	0.133
History of PONV *(n)*	3	1	6	0.13
Prior spine surgeries *(n)*	54	52	64	0.083
Preoperative pain (VRS)	3.2±2.5	4±2.4	4.2±2.8	0.059
Medications prior to admission				
NSAIDs *(n)*	25	34	32	0.312
Acetaminophen *(n)*	48	50	49	0.939
Muscle relaxant *(n)*	16	23	12	0.121
Morphine Equivalents (mg)	31 ± 46	48 ± 65	76±70 Ω	< 0.0001

Numbers (n), means values ± standard deviation *(± SD)*. Significant p-value ≤ 0.05.

BMI (body mass index), ASA (American Association of Anesthesiologist), PONV (postoperative nausea and vomiting), VRS (Verbal Rating Scale), NSAIDs (non-steroidal anti-inflammatory drugs).

Ω compared between the three groups.

† Compared to Ketamine group.

‡ Compared to Methadone group.

* Compared to Ketamine + Methadone group.

Intraoperative characteristics are displayed in table 2. Intra-operatively, the ketamine + methadone group had significantly more subjects (n) received IV acetaminophen (p<0.0001) and less morphine equivalents (p<0.0001).

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Table 2: Duration of surgery, duration of anesthesia, and intraoperative drug administration among the three groups

	Ketamine (n = 90)	Methadone (n = 90)	Ketamine + Methadone (n = 88)	p-value
Surgery Duration (min)	192±102	213±101	224±124	0.142
Anesthesia Duration (min)	250±108	264 ± 110	289 ± 134	0.78
Midazolam *(n)*	33‡*	82 Ω	67†‡	< 0.0001
Intraoperative medications				
IV Acetaminophen *(n)*	60	45*	77 Ω	< 0.0001
Ketamine *(mg)*	70 ± 36	--	71 ± 38	--
Methadone *(n)*	--	17 ± 9	17 ± 9	--
Ketorolac *(n)*	4	5	4	0.929
Morphine Equivalents (mg)	25 ± 58	28 ± 39	12 ± 26 Ω	< 0.0001

Numbers (n), means values ± standard deviation *(± SD)*. Significant p-value ≤ 0.05
Ω compared between the three groups
† Compared to Ketamine group.
‡ Compared to Methadone group.
* Compared to Ketamine + Methadone group.

PACU assessments are found in table 3. In PACU the methadone + ketamine group had a statistically significant: (a) higher initial VRS pain score (p<0.0001), (b) less subjects (n) received IV acetaminophen (p=0.0003), (c) more subjects (n) received ketamine (p=0.0003), (d) subjects required the larger amount of morphine equivalents (mg) (p=0.0005) and (e) reported more side-effects with urinary retention (p=0.034) and constipation (p<0.0001) among the three groups.

Table 3: PACU characteristics and number of patients requiring pain medication among the three groups.

PACU	Ketamine (n = 90)	Methadone (n = 90)	Ketamine + Methadone (n = 88)	p-value
Length of Stay (min)	154 ± 71	175 ± 144	164 ± 73	0.399
Pain on arriving in PACU (VRS)	4 ± 4	5 ± 4	7 ± 3 Ω	< 0.0001
PACU medications				
Acetaminophen *(n)*	13	27 Ω	8	0.0008
NSAIDs *(n)*	2	3	1	0.63
Muscle Relaxants *(n)*	17	14	22	0.24
Benzodiazepines *(n)*	1	2	6	0.08
Antiemetics *(n)*	5	8	3	0.316
Ketamine *(n)*	4	6	16 Ω	0.003
Naloxone *(n)*	1	4	2	0.37
Morphine Equivalents (mg)	7 ± 7	12 ± 15	26 ± 43 Ω	< 0.0001
Side effects				
Nausea *(n)*	22	16	20	0.52
Vomiting *(n)*	5	1	3	0.26

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Urinary Retention *(n)*	5	6	14 Ω	0.031
Constipation *(n)*	10	7	31 Ω	< 0.0001

Numbers (n), means values ± standard deviation *(± SD)*. Significant p-value ≤ 0.05
Pain verbal rating scale (VRS) scores: 0 = none to 10 = intolerable pain.
Ω Compared between the three groups
† Compared to Ketamine group.
‡ Compared to Methadone group.
* Compared to Ketamine + Methadone group.

Hospital course at 24-, 48-, and 72-hours for pain medication requirements are included in table 4.

During the hospital stay at 24, 48, and 72 hours post-op the ketamine + methadone group compared to the methadone alone and ketamine alone groups had statistically significant more subjects who required: (a) muscle relaxants at all three time points ($p<0.0001$), (b) neuropathic medications at 24,48 ($p<0.0001$), and 72 hours ($p<0.0006$) (c) ketamine at 24, 48 ($p<0.0001$) and 72 hours($p=0.0055$), (c) naloxone at 24 hours ($p=0.0028$), (d) benzodiazepines ($p=0.017$) (e) higher doses of morphine equivalents at all three time points ($p<0.0001$). At 72-hours post-op, the methadone group significantly had less subjects (n) who received ($p < 0.05$) among the three groups.

Table 4: Hospital course and number of patients who required pain medications at 24, 48, and 72 hours post-operatively among the three groups.

Post-operative medications	Ketamine (n = 90)	Methadone (n = 90)	Ketamine + Methadone (n = 88)	p-value
24 hours				
Acetaminophen *(n)*	64	73	68	0.316
NSAIDs *(n)*	3	5	7	0.407
Muscle Relaxants *(n)*	49	48	69 Ω	< 0.0001
Neuropathic *(n)*	26	19	51 Ω	< 0.0001
Lidocaine Patch *(n)*	2	0	6	
Benzodiazepines *(n)*	12	6	13	0.185
Antiemetics *(n)*	15	19	24	0.222
Ketamine *(n)*	7	6	24 Ω	< 0.0001
Naloxone *(n)*	3	4	11 Ω	0.027
Morphine Equivalents (mg)	67 ± 51	80 ± 68	170±257 Ω	< 0.0001
48 hours				
Acetaminophen *(n)*	55	61	64	0.952
NSAIDs *(n)*	1	4	6	0.222
Muscle Relaxants *(n)*	39	33	67 Ω	< 0.0001
Neuropathic *(n)*	23	17	44 Ω	< 0.0001
Lidocaine Patch *(n)*	1	1	3	0.508
Benzodiazepines *(n)*	12	5	18	0.207
Antiemetics *(n)*	12	7	13	0.319
Ketamine *(n)*	6	4	23 Ω	< 0.0001
Naloxone *(n)*	5	4	10	0.239
Morphine Equivalents (mg)	74 ± 57	92 ± 89	172±171 Ω	< 0.0001
72 hours				

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Acetaminophen *(n)*	38	50	53	0.198
NSAIDs *(n)*	0	1	3	0.217
Muscle Relaxants *(n)*	29	25	51 Ω	0.0001
Neuropathic *(n)*	17	19	36 Ω	0.007
Lidocaine Patch *(n)*	1	1	1	0.994
Benzodiazepines *(n)*	10	3†*	15 Ω	0.017
Antiemetics *(n)*	8	6	13	0.292
Ketamine *(n)*	3	3	13 Ω	0.006
Naloxone *(n)*	4	3	9	0.182
Morphine Equivalents (mg)	71 ± 59	87 ± 87	188±218 Ω	< 0.0001

Table 5: Pain scores (VRS) at 24, 48, and 72 hours post-operatively and total length of stay among the three groups.

	Ketamine (n = 90)	Methadone (n = 90)	Ketamine + Methadone (n = 88)	p-value
24 hours VRS Pain Score	5 ± 2	5 ± 2	6 ± 2 Ω	< 0.0001
48 hours VRS Pain Score	5 ± 2	5 ± 2	6 ± 2 Ω	< 0.0001
72 hours VRS Pain Score	5 ± 2	5 ± 2	6 ± 2 Ω	< 0.0001
Total Length of Stay (days)	4 ± 3	4 ± 3	5 ± 3 Ω	< 0.0001

Numbers (n), means values ± standard deviation *(± SD)*. Significant p-value ≤ 0.05
Pain verbal rating scale (VRS) scores: 0 = none to 10 = intolerable pain.
Ω Compared between the three groups
† Compared to Ketamine group.
‡ Compared to Methadone group.
* Compared to Ketamine + Methadone group.

At 24-, 48-, and 72-hours post-op, the VRS pain scores (Table 5) were significantly larger in the ketamine + methadone group ($p<0.0001$).

methadone, in producing antinociception, which is the relief from pain. From these findings, the main objective in this study was to see if the use of both ketamine and methadone would offer a synergetic modality to reduce postoperative pain and opioid consumption for patients undergoing elective lumbar spine surgery [13].

A previous meta-analysis studying the prevalence and risk factors for opioid use after spine surgery showed that pre-operative opioid users and patients with pre-existing depression or anxiety have a statistically significant higher odds of long-term opioid use [14]. This could have predisposed the patients to (1) An inherent increased risk for postoperative pain, and (2) An increased dependency on pain medications to manage the pain. The ketamine + methadone group was also found to have higher PACU VRS pain scores and a lengthier PACU stay. In a double-blind randomized study, 22 patients who were administered sevoflurane-remifentanil anesthesia were divided into two groups: the first group received a ketamine bolus followed by methadone and ketamine infusions, while the second group received a saline bolus and a methadone infusion only [15]. The study found that the methadone + ketamine group had higher requirements for opioids (p=0.004). Additionally, patients in the methadone + ketamine group received 70% less methadone via patient-controlled analgesia at the 24-hour mark (p=0.001) [15]. The ketamine + methadone group also received the lowest dosage of intraoperative opioids. It is worth mentioning that this could potentially lead to insufficient pain management for the patient, resulting in heightened post-procedural pain and the need for additional pain medications. These data also confirm that opioid analgesics are better at relieving acute pain than either ketamine or methadone. We did not find existing articles specifically addressing the relationship between the duration of spine procedures and the requirements for postoperative pain medication. This differs from a previous randomized control trial similar study by Murphy et al. [16], which studied (127 patients) the use of methadone and ketamine together when compared to methadone alone. Patients in the methadone and ketamine group required significantly less opioid dosage on the first and second postoperative day ($p<0.001$) and reported lower pain scores during the first 3 postoperative days, compared to those given methadone alone. These results suggested that postoperative analgesia

can be significantly enhanced in this patient population by using a combination of agents that act on both the NMDA and μ-opioid receptors.

A previous meta-analysis (2021) showed that there were significant improvements in resting pain scores at 4, 12, and 24 hours post-operatively in ketamine patients compared to placebo [7] in our study, the data from the ketamine group demonstrates that the pain scores at 24, 48, and 72 hours were comparable to the methadone and were significantly less than the ketamine + methadone group. Additionally, methadone has been shown to reduce pain scores at the 48-hour mark but not at 24-hours, while also effectively decreasing the requirement for opioids following surgery [9]. Our data showed that the methadone group at 24-, 48-, and 72-hours were significantly less than the ketamine + methadone group.

Conclusion

These retrospective findings suggest that the combined use of ketamine + methadone did not improve postoperative pain control compared to use of either drug alone for intraoperative analgesia in a patient population undergoing spine surgery. These negative findings were likely related to greater chronic opioid use in the preoperative period and number of prior spine operations by patients in the combination group. The ketamine + methadone group had the highest pain scores post-operatively and the most side-effects, including urination retention and constipation. Future prospective studies should evaluate the adjunctive use of ketamine and methadone alone and in combination for intraoperative analgesia in non-opioid dependent patients.

References

1. Prabhakar NK, Chadwick AL, Nwaneshiudu C, et al. Management of Postoperative Pain in Patients Following Spine Surgery: A Narrative Review. Int J Gen Med 15 (2022): 4535-4549.
2. Nwosu ADG, Chukwu LC, Onwuasoigwe O, et al. Redefining the Role of Analgesic Adjuvants in Pain Management: A Narrative Review. Indian Journal of Pain 37 (2023): 65-73.
3. Ghai B, Jafra A, Bhatia N, et al. Opioid sparing strategies for perioperative pain management other than regional anaesthesia: A narrative review. J Anaesthesiol Clin Pharmacol 38 (2022): 3-10.
4. Inturrisi CE. Clinical pharmacology of opioids for pain. Clin J Pain 18 (2002): S3-13.
5. Gourlay GK, Wilson PR, Glynn CJ. Pharmacodynamics and pharmacokinetics of methadone during the perioperative period. Anesthesiology 57 (1982): 458-467.
6. Bell RF, Dahl JB, Moore RA, et al. Perioperative ketamine for acute postoperative pain. Cochrane Database Syst Rev 10 (2006): CD004603.
7. Wang X, Lin C, Lan L, et al. Perioperative intravenous S-ketamine for acute postoperative pain in adults: A systematic review and meta-analysis. Journal of Clinical Anesthesia 68 (2021):110071.
8. Loftus RW, Yeager MP, Clark JA, et al. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. Anesthesiology 113 (2010): 639-646.
9. Gourlay GK, Willis RJ, Lamberty J. A double-blind comparison of the efficacy of methadone and morphine in postoperative pain control. Anesthesiology 64 (1986): 322-327.
10. Chui PT, Gin T. A double-blind randomised trial comparing postoperative analgesia after perioperative loading doses of methadone or morphine. Anaesth Intensive Care 20 (1992): 46-51.
11. Lynch, ME. A Review of the Use of Methadone for the Treatment of Noncancer Pain. Pain Res Manage 10 (2005): 133-144.
12. Pelissier T, Laurido C, Kramer V, et al. Antinociceptive interactions of ketamine with morphine or methadone in mononeuropathic rats. Eur J Pharmacol 477 (2003): 23-28.
13. Kharasch ED, Clark JD. Methadone and Ketamine: Boosting Benefits and Still More to Learn. Anesthesiology 134 (2021): 676-679.
14. Lo YT. Long-Term Opioid Prescriptions After Spine Surgery: A Meta-Analysis of Prevalence and Risk Factors. World Neurosurgery 141 (2020): e894-e920.
15. Pacreu S, Fernández Candil J, Moltó L, et al. The perioperative combination of methadone and ketamine reduces postoperative opioid usage compared with methadone alone. Acta Anaesthesiol Scand 56 (2012): 1250-1256.
16. Murphy GS, Avram MJ, Greenberg SB, et al. Perioperative Methadone and Ketamine for Postoperative Pain Control in Spinal Surgical Patients: A Randomized, Double-blind, Placebo-controlled Trial. Anesthesiology 134 (2021): 697-708.

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