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Research Article

Intraoperative Intravenous Methadone and Ketamine Combination versus Intravenous Morphine and Ketamine Combination for Post-Operative Analgesia in Patients Undergoing Lower Extremity Fracture Surgery

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Abstract:

Background: Pain management for lower extremity fracture surgeries can be challenging. The purpose of this study is to determine whether the use of ketamine and methadone are more effective than ketamine and morphine to reduce postoperative pain and morphine requirements in patients undergoing lower extremity fracture surgery.

Materials and Methods: Seventy-five patients 18-65 years of age, ASA class I-III, were enrolled in this study, which scheduled for elective lower extremity orthopedic surgery involving fracture of femur or tibia were recruited for the study. Thirty-eight randomized to the Methadone group and 37 randomized into the Morphine group.

Participants were randomized to either one of the two groups: methadone (2ug/kg fentanyl, 0.2 mg/kg ketamine and 0.2 mg/kg methadone IV) versus control (2 ug/kg fentanyl, 0.2mg/kg ketamine and 0.2 mg/kg morphine IV). The primary outcome was total morphine equivalent (MEQ) during the first 24 and 48 hours after surgery. Secondary outcomes included postoperative pain scores in PACU, at 24 and 48 hours, as well as postoperative nausea and vomiting (PONV).

Results: There was no difference in intraoperative consumption of fentanyl between the Methadone group 360mcg and Morphine group 344mcg. In the first 24 hours postoperatively, the Methadone group consumed less MEQ compared with the Morphine group (36.1 mg vs 54.8 mg, p=0.0072), showed lower pain scores than the Morphine group (p=0.0146), and experienced more nausea and vomiting than the Morphine group. There were no differences in sedation in both groups.

Conclusion: The intraoperative use of intravenous methadone significantly reduced post-operative opioid requirement in patients undergoing lower extremity fracture surgery. The results also demonstrated the methadone group had a higher rate of PONV.

Keywords: Intravenous, Methadone, Ketamine, Morphine, Lower Extremity Fracture, Pain Control

Introduction

Postoperative pain resulting from lower extremity fracture surgeries especially tibia fractures can be excruciating, sometimes lasting for several days after hospital discharge. Pain management in these patients can be a challenge to both anesthesia providers and orthopedic surgeons. Undertreated moderate-to-severe post-surgical pain can predispose patients to persistent pathologic or chronic pain states and cause significant morbidity and disability [1, 4].

Intravenous morphine is the traditional opioid used for perioperative pain control in surgical patients but by itself it is not very effective in controlling movement pain. Therefore, it is often combined with NMDA antagonists to treat movement related acute pain that may have beneficial effects on chronic postoperative pain [5-10].

Methadone is a synthetic opioid with mu receptor agonist like morphine and has NMDA receptor antagonist activity like ketamine [11-13]. Methadone is attractive as a peri-operative analgesic due to its rapid onset

of action, long elimination half-life, which provides prolonged analgesia to treat persistent pain, and its NMDA antagonism, which treats neuropathic component of pain and may prevent opioid tolerance and opioid induced hyperalgesia. Methadone has been successfully and safely used in patients undergoing spine surgery, laparoscopic surgery and cardiac surgery, resulting in improved postoperative pain control [14, 15]. In addition, methadone has been shown to provide superior pain control than morphine in patients undergoing upper abdominal surgery, total hip arthroplasty and cesarean delivery [16, 17]. Lower extremity surgery can have moderate to severe pain, needing large doses of opioids and patients often become tolerant to these opioids. Surgeons prefer no regional anesthesia for lower extremity surgery due to risk of compartment syndrome because of the tight muscle compartments in thigh and calf [18].

We performed this randomized controlled study to test the hypothesis that ketamine and methadone are more effective than ketamine and morphine to reduce postoperative pain and postoperative morphine requirements.

Materials and Methods:

This study was performed at the University of Louisville Hospital. The University of Louisville Human Studies Committee approved the protocol, and all participants gave written informed consent before participating in the study. This trial was registered with Clinicaltrials.gov with identifier NCT00892606.

The study included consecutive patients with ages between 18-65 years with ASA class I-III, who presented for elective lower extremity orthopedic surgery involving fracture of long bones (femur or tibia) and expected to last more than one hour. Patients with any known contraindications to methadone or morphine were excluded. This included hypothyroidism, Addison's disease, prostatic hypertrophy, known hepatic or renal dysfunction or urethral stricture. Pregnant patients, patients with BMI more than 35 or known respiratory or cardiovascular function were also excluded. Patients taking drugs that induce or inhibit p450 enzyme systems or who needed opioids in the two weeks before surgery were excluded. A preoperative EKG was done on all patients to assess the baseline QT_c and if prolonged (>450 msec), they were excluded from the study.

Experimental design:

Statistics: A power analysis was performed -to measure a 40% reduction of morphine consumption in the first 48 hours postoperatively in the methadone group, a 38 patients in each group were needed to achieve 90% power at a significance level of 0.05. Summary statistics on the demographic and outcome data were expressed as means +/- SD for continuous values and percentage for the categorical values. A two-way ANOVA using repeated measures was used to analyze the data and adjusted Tukey's test. All analyses were performed using SAS version 9.3 and with a statistical significance of 0.05.

The randomization codes were computer-generated and stored in opaque envelopes until opened. The unblinded investigator opened the randomization envelope to determine patient group assignment after informed consent was obtained. The patients were randomized to one of two groups: Patients in methadone group received 2 µg/kg fentanyl, 0.2 mg/kg ketamine and 0.2 mg/kg of methadone IV and patients in the control group received 0.2 mg/kg ketamine, 2 µg/kg fentanyl and 0.2 mg/kg of morphine IV with induction of general anesthesia. Methadone and morphine were administered after the patient was intubated successfully as confirmed by end tidal carbon dioxide.

Patients received 1- 4 mg midazolam before being transferred to the operating room, at the discretion of the anesthesia care team not involved in the study. All patients were monitored with standard ASA monitors. The anesthesia provider (resident/certified registered nurse anesthetist/attending) and the research fellow who followed the patient (2^{nd} investigator) in the PACU were blinded to the study drug given to the patient.

Patients were anesthetized with propofol 2 mg/kg or etomidate 0.2 mg/kg, 0.2 mg/kg of ketamine and rocuronium 1 mg/kg, per the anesthesia provider. After intubation, the study drug (0.2 mg/kg of morphine or methadone diluted to 10cc) was administered by the blinded anesthesia provider to the patient. Anesthesia was maintained with oxygen, air and an inhalational agent of anesthesiologist's choice to a targeted BIS between 40 and 60. Additional analgesia was provided with fentanyl in 50 µg increments at the discretion of the anesthesiologist. At the end of surgery, the neuromuscular block was reversed and fentanyl was titrated to maintain a spontaneous respiratory rate of 12-15 breaths per minute and 8-10 ml/Kg tidal volumes to meet extubation criteria. The intraoperative use of narcotics, sedatives and anesthetic drugs were recorded. The type of surgery, duration of surgery and use of additional analgesics and antiemetics were noted.

An investigator blinded to randomization tracked the patients in the PACU. In the recovery room, morphine was given in 2-4 mg increments intravenously up to a total of 20 mg, if they reported a verbal rating pain scale (VRS) more than 4. If the patients continued to report pain (VRS > 4) after 20 mg morphine was given, intravenous hydromorphone was given in 0.5 mg dose every 15 minutes (maximum dose 4 mg) until the patient had adequate analgesia (VRS < 4). Patients received morphine patient-controlled analgesia (PCA) for pain relief as the primary analgesic. The PCA was adjusted at 1 mg morphine with a 6-minute interval lockout and 10 mg/ hour maximum dose. Acetaminophen and oxycodone combination 500 mg/5 mg were prescribed on the floor as needed, to maintain VRS < 4.

In the PACU, vital signs including respiratory rate, heart rate, non-invasive blood pressure (NIBP), sedation score and oxygen saturation were recorded every 15 minutes. VRS for pain were obtained from the patient every 15 minutes until the patient was discharged to the floor. The investigator also recorded the sedation scores every 15 minutes using the following scale until patient was discharged to the floor:

0-Patient is fully alert

1-Patient has intermittent sedation

2-Patient sedated but responsive to verbal stimuli

3-Patient unresponsive to verbal stimuli

Patients were seen at 8 am and 4 pm on postoperative day one and two and at 8 am on the morning of postoperative day three after surgery, if they were still in the hospital. The initial dose of rescue analgesics and time it was given and was recorded. VRS at rest and on movement was recorded, when the patients were seen. Morphine equivalent required during the first 24 and 48 hours after surgery, as well as incidence and severity of postoperative nausea and vomiting (PONV) was recorded.

Our primary outcome was total morphine equivalent (MEQ) consumption during the first 48 hours after surgery. The secondary outcomes were pain scores in PACU, the worst pain scores in the first 24 hours and 48 hours and time to initial dose of rescue analgesic. Respiratory rate to detect respiratory depression and PONV were recorded.

Results:

Seventy five patients were included in this randomized study with 38 patients receiving Methadone with ketamine and 37 receiving Morphine with ketamine. One patient in the methadone/ketamine incorrectly received morphine (This patient should excluded from statistical analysis); however, this patient is included in the group to which they

were randomized, for intent to treat analysis. All patients are available for follow-up during recovery and the first 24 hours periods; however, in the second 24 hours period, 4 and 5 patients were lost to follow-up in the Morphine and Methadone groups, respectively.

Demographic data are presented in Table 1.The average age and BMI were comparable for the Morphine and Methadone groups. There were more males in both the Methadone and the morphine groups. The intraoperative fentanyl use was 344 μg for the morphine group and 360 μg for the methadone group. (Table 1)

	Methadone (n = 38)		Morphine (n = 39)
Age (y)	37.18±13.72		34.51±11.59
Sex			
Male	84.2%		74.4%
Female	15.8%		25.6%
Body mass index (mg/k^2)	27.74±4.05		26.95±4.77
Intraoperative Fentanyl (mcg)	360.05±171.67		344.23±146.17
Values are expressed as mean±SD, and percentage as appropriate.			
† *P*< 0.05.			

Table 1: *Demographic and Intraoperative Data of the Study Population*

Peri-Induction consumption of sedatives and analgesics was not different between the Morphine and the Methadone groups. (Table 2.)

	Morphine Group	Methadone Group
Preoperative Midazolam (mg)	2.36	2.26
Intraoperative Fentanyl (mg)	140	174
Intraoperative Ketamine (mg)	16	17.2

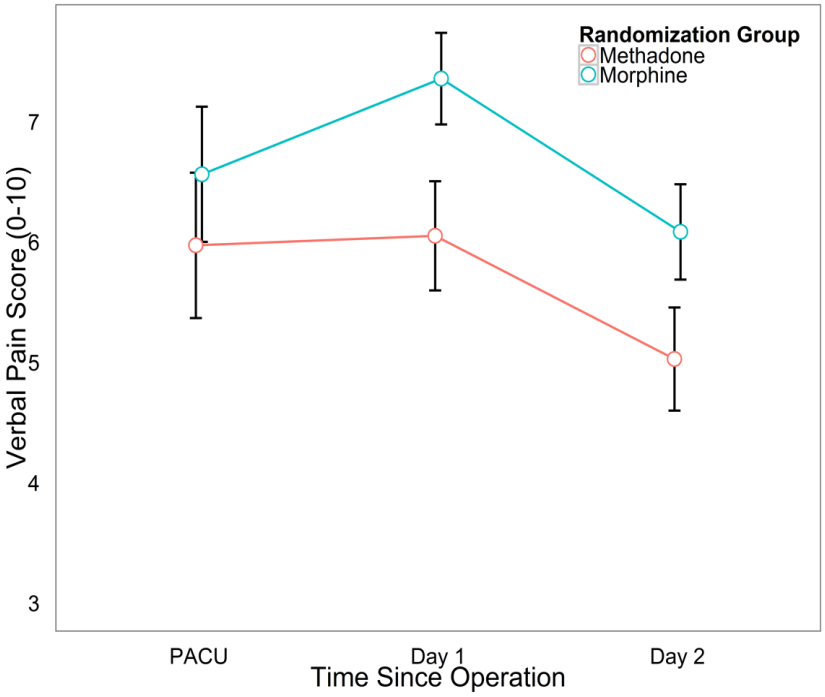
Table 2: *Intraoperative Consumption*

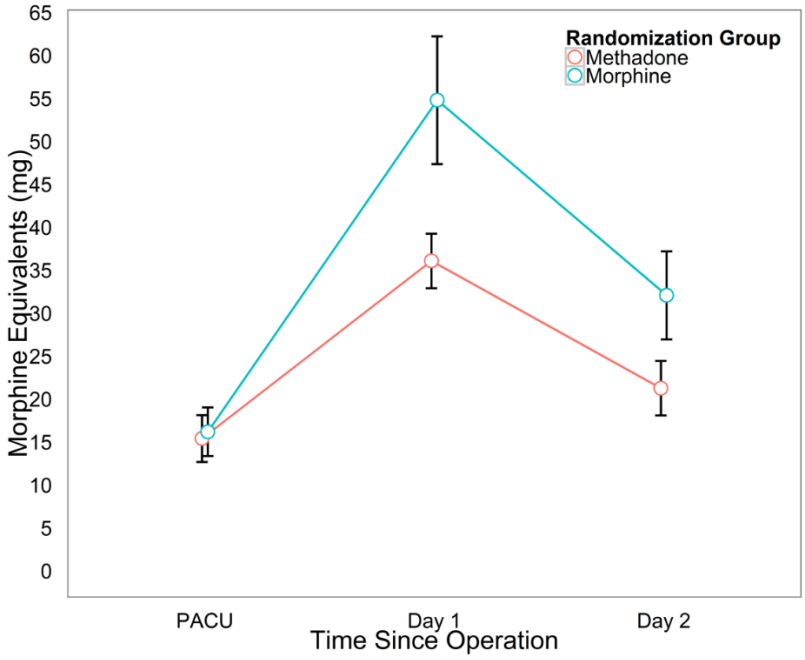
Post-operative morphine equivalents consumption differed significantly during the first 24 post-operative hours (p=0.0031); however, there were no detectable differences in VRS during recovery or the post-operative period. The Methadone group consumed less morphine equivalents (MEQ) than the Morphine group (36.1 mg vs 54.8 mg) at 24 hours (Table 3).

	Morphine Group	Methadone Group
	Mean +/_ SD	Mean +/_ SD
Verbal Rating Scale in recovery room (0-10)	7 ± 4	6 ± 4
Morphine consumption in recovery room (mg)	16 ± 18	15 ± 17
Incidence of PONV (%)	0	0
Verbal Rating Scale at 24 hours (0-10)	7 ± 2	6 ± 3
Morphine Consumption at 24 hours (mg)	54.8 ± 46	36.1 ± 20
Incidence of PONV (%)	3%	29%
Verbal Rating Scale at 48 hours (0-10)	6 ± 2	5 ± 3
Morphine consumption at 48 hours (mg)	32 ± 31	21 ± 18
Incidence of PONV (%)	5%	9%

Table 3: *Post-Operative Outcomes*

For each group and by time period, Figures 1 and 2 show the average morphine equivalents consumed and verbal rating sale (0-10), respectively. Overall, the Morphine group consumed more morphine equivalents (p = 0.0072) and showed higher pain scores (p = 0.0146) compared to the Methadone group. Additionally, the figures show a relationship between increased morphine equivalent consumption and worse pain scores.





In the first 24 post-operative hours, the Methadone group showed higher rates of nausea/vomiting than the following 24-hour period (29.0% vs. 9.1%, p=0.004), Table 3). The Morphine group had a lower incidence of postoperative nausea and vomiting in the first 24 hours after surgery but the incidence of nausea/vomiting doubled from 24 to 48 hours (2.6% vs 5.4%, Table 3).

Patients' vital signs were also measured in recovery and compared. No differences were found in MAP_Q30 (98.1 vs 95.8), MAP_Q60 (96.7 vs. 98.1), SPO2_Q30 (97.9 vs. 97.7), SPO2_Q60 (97.9 vs. 97.9) for the Methadone and Morphine groups, respectively. Sedation levels were tracked at 30 and 60 minutes in recovery and during the first and second 24-hour post-operative periods. At all time periods, there were no differences in sedation; however, levels of sedation decreased significantly at each visit ($p < 0.0001$).

Discussion:

The main finding of this study was that the addition of intraoperative methadone to ketamine significantly decreased postoperative opioid requirements compared to morphine combined with ketamine.

Ketamine, a NMDA antagonist, binds non-competitively to phencyclidine binding site of NMDA receptor in low analgesic or sub anesthetic doses, acted synergistically with opioids and produces better quality of analgesia and opioid sparing effect in a variety of painful surgical procedures [8,14]. Given the severe and difficult to control pain observed in lower extremity

fracture surgery in the immediate postoperative period, it is important to investigate effective combinations and regimens that would benefit patients without use of regional anesthesia. Regional anesthesia is relatively contraindicated in these patients because of the possibility of compartment syndrome that can go unrecognized.

Methadone is a synthetic opioid with mu receptor agonist an receptor antagonist activity. It has long been associated with the treatment of addiction to heroin. There has been a resurgence of interest in the use of methadone as a perioperative analgesic agent within the last decade. In addition, it prevents reuptake of serotonin and norepinephrine. It is commercially available as a racemic mixture of a D- and L-isomer compounds, each optical isomer has distinct opioid receptor affinity but the L –isomer is more physiologically active [19]. Methadone has a variable bioavailability of 40-99 % after oral administration that can potentially lead to serious side effect [19, 20]. It has an oral to parenteral potency ratio of 1: 2 with a long plasma half-life, approximately 24-48 hours (but has a wide inter-individual variability of 13-50 hours), when larger doses are given (≥ 20 mg). The onset of action of intravenous methadone is rapid and comparable to the onset of action of fentanyl and sufentanil [15]. The duration of analgesic effect approximates the half-life of the drug (24-48 hours). It is lipid soluble and has high binding to plasma proteins [16]. These properties of intravenous methadone make it an attractive peri-operative analgesic due to its rapid onset of action, long elimination half-life and its NMDA antagonism, which treats movement pain and prevents opioid tolerance and hyperalgesia. Methadone is primarily eliminated by metabolism and has no active metabolites, unlike morphine and other opioids. A single dose does not cause accumulation. However, one important issue which can arise during methadone treatment is related to its high variability in metabolism [17].The CYP3A4 enzyme found mainly in the liver and in the intestines, metabolizes methadone. The 1-30 fold variability in methadone metabolism is attributed to the variability of expression of this enzyme. Because methadone is mainly metabolized in the liver, it is subject to changes in metabolism by drugs that induce or inhibit the CYP3A4 enzyme such as antifungal and antiretroviral drugs, barbiturates, dexamethasone, and macrolide antibiotics [17]. This can lead to potentially higher levels than expected.

Methadone is proven to be efficacious as a perioperative analgesic in a variety of surgeries like laparoscopic, complex spine and cardiac surgery-all with high degree of pain (Gourlay et al., 1982) [13-15, 22]. They also had significantly less nausea and vomiting compared with morphine group [23]. The results of our study are comparable to studies with published data in terms of pain relief but our patients had a higher rate of PONV [24].

Patients with lower extremity surgery benefit from having a long acting opioid like methadone, because of severe and prolonged pain associated with these procedures and inability to provide regional anesthesia for them. The higher incidence of postoperative nausea and vomiting may limit its use, but more studies may needed to be performed to determine effects of using supra prophylaxis of anti-emetic therapy with the use of methadone. In our study, we used a standard anti-emetic prophylaxis that was proportionate to the risk profile of the patient. None of our patients had obstructive sleep apnea and we cannot comment on the effects of methadone in patients with obstructive sleep apnea. In our study, we did not observe an increased risk of respiratory depression for the 24-48 hours period.

Although the patients self-administered PCA to reach a VRS score of 6-7, which is higher pain score than acceptable, patients needed less morphine to reach that pain score. We believe that when patients are in extreme pain, they may not aim for VRS scores of less than 4 and they create self-expectations of higher pain scores.

Our study has several limitations that decrease the generalizability of its results. This was single center study in an academic tertiary care center. It is unclear whether the results can be generalized to other settings. We compared methadone and ketamine to methadone and morphine. It is unknown whether the results would be the same for other narcotics and whether the addition of ketamine altered the outcome. We did not follow the long-term outcomes at 30 and 60 days to see if there was any difference in the incidence of chronic pain.

Conclusions

Patients benefit from receiving longer acting opioids like methadone in combination with ketamine when compared with morphine and ketamine. They need substantially less morphine equivalent to reach and maintain the same verbal rating score analogue scale on pain scores.

Conflict of Interests: No potential conflict of interest relevant to this manuscript was reported.

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