Original Research

Effect Of Adding Intravenous Ketamine To Methadone For Postoperative Pain In Opioid Addicts After Major Surgery: A Double-Blind Randomized Control Clinical Trial Study

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Abstract

Background: The purpose of this study is to investigate the effect of adding intravenous ketamine to methadone in controlling the pain of opium-addicted patients after major surgery in the intensive care unit (ICU) of Shahid Mohammadi Hospital.

Methods: In a rigorously controlled clinical investigation, a randomized, double-blinded study design was employed to evaluate a total of 89 opium-addicted patients were included in the study after major surgery in the Shahid Mohammadi Hospital, Hormozgan University of Medical Sciences, Bandar Abbas, Iran. Richmond Agitation-Sedation Scale (RASS) and pain intensity were measured repeatedly till 24 hours.

Results: Eighty-nine patients were included in this study. Intervention and control groups need for morphine was statistically different. Average pain of study groups varied at 1, 6, 12, and 24 hours after surgery ($P<0.05$), as well as the average RASS ($P<0.05$), both RASS and pain indices were lower in intervention group than controls.

Conclusion: The findings of the current investigation reveal that adding intravenous ketamine to methadone controls pain and reduces the need for morphine in opium-addicted patients after major surgery in the intensive care unit without serious side effects. Therefore, this combination can be used in this group of patients to reduce pain and reduce recovery time.

Keywords: Ketamine, Methadone, Pain, Addicted patients, Opium, Intensive Care Unit.

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Introduction

Pain is a sensory experience caused by tissue damage (1). In surgery, due to skin incision and damage and stretching of the involved tissue or cutting of nerve fibers, pain receptors, stimulation and pain sensation are created (2). This feeling of pain is very annoying for the patient after the operation (3). Postoperative pain is caused by tissue damage. In addition to the suffering of the patient, it can cause anxiety, insomnia, fear and irritability of the patient's nervous system and cause a delay in the discharge of the patient and increase the cost of treatment (4). Therefore, effective pain control is essential for ideal care of patients undergoing surgery (5). Ketamine is an inhalant anesthetic drug and a derivative of phencyclidine, which has been used clinically since the 1990s. Ketamine mainly exerts its effects with the non-competitive antagonist of the NMDA glutamate receptor by binding to the phencyclidine binding site. Ketamine is one of the few anesthetic drugs that provides all three components required for optimal anesthesia. Ketamine does not suppress the central response to the increase of carbon dioxide, it usually preserves the pharyngeal-larynx reflexes and causes bronchodilation. In anesthesia with ketamine, skeletal muscle tone and airway secretions increase. The most important side effect of systemic ketamine is emergency reactions, which has reduced its clinical use (6-8). This phenomenon occurs in 15% of patients and is almost always mild. This complication usually occurs in the form of real dreams, hallucinations and delusions. Some patients have nightmares for a few days after taking the medicine. Less than 1-2% of patients suffer from severe emergency restlessness. Usually, this complication is likely to occur 24 hours after surgery. Some studies have shown that the simultaneous administration of benzodiazepines with the administration of ketamine reduces the prevalence of this phenomenon (8-10). Other side effects of ketamine include temporary apnea, cardiovascular complications, laryngospasm and vomiting. Although these side effects are also uncommon; But following rapid intravenous administration, high doses of ketamine occur more often (6-7). Slow drug administration at a rate of 5/mg/kg/min. can reduce the prevalence of these complications (11). Ketamine increases tracheal-bronchial and salivary secretions. In young children and patients undergoing airway examination (fiberoptic laryngoscopy), pretreatment with anticholinergic drugs 10 minutes before ketamine administration can be beneficial (8). Nausea and vomiting after regaining consciousness are also commonly seen; But it is generally short-term and responds well to anti-emetic drugs (12). Methadone is known as a widely used synthetic opioid with high potency in the clinic. This drug is used in the treatment of opioid use disorder, control of opioid withdrawal syndrome, and treatment of chronic pain. The plasma half-life of this drug is different in different Patients and can vary from 8 to 59 hours. Despite this feature, due to the variability of the pharmacokinetics of this drug in different Patients, in order to maintain the therapeutic effects of the drug, it is usually necessary to take the drug in divided form (13). Methadone is a mu opioid receptor agonist and a compound painkiller, and it has stronger adhesion to opioid receptors than opium and its derivatives. Using it as a well-known and standard method can help reduce the damage and demand of the consumer (14). Lack of proper pain control prolongs the hospitalization time of patients and imposes more treatment costs on the patient and the treatment system. Therefore, the aim of this study is to investigate the effect of adding intravenous ketamine to methadone in controlling the pain of opium-addicted patients after major surgery in the Shahid Mohammadi Hospital.

Methods

This was a double-blind randomized clinical trial. The study population is opium-addicted or ASA class I or II patients aged 18 to 75 who undergo major elective surgery at Shahid Mohammadi Hospital, Hormozgan University of Medical Sciences, Bandar Abbas, Iran, between September

2023 and March 2024. The inclusion criteria were Patients aged 18 to 75 years who are addicted to opium have informed consent. The exclusion criteria were Patient dissatisfaction, sensitivity to methadone, sensitivity to ketamine, kidney failure, liver failure, patients with increased intracranial pressure, head trauma, history of epilepsy, heart diseases, patients with unstable hemodynamic status, history of daily drug use in the past six months.

After obtaining written informed consent all patients underwent standard monitoring of respiratory (respiratory rate), cardiovascular (electrocardiogram and pulse rate), and blood pressure monitoring and appropriate venous access.

Patients were classified into two groups. The first group of patients who only methadone with a dose of 5 mg/kg (based on ideal weight). received intramuscularly every 12 hours for analgesia (group M). The second group of patients who received methadone with ketamine at a dose of 5 mg/kg (based on ideal weight). every 12 hours they were given intravenously for analgesia. (M+K group). It should be noted that the maximum dose of ketamine is 10mg/IM. Then, the pain level of the patients after the operation was evaluated through the VAS standard at 1, 6, 12, 24 hours after the operation, in the critical care unit. The amount of patients' need for additional narcotic (morphine) and the incidence of nausea, vomiting and Pruritus in patients, as well as BP, HR of patients were recorded at certain hours. If the pain intensity according to the VAS criterion was>3, the patient received morphine at a dose of 5 mg. RASS criterion which is used to evaluate the level of relaxation and irritability of patients hospitalized in ICU. It is a 10-point scale that includes 4 levels for the level of irritability and anxiety (1 to 4), one level that indicates alertness (0 to 1) and 5 levels for the level of relaxation and sedation (-1 to -5). A score of 1 to 4 indicates the level of irritability, and from -5 to -1 indicates an increase in the level of relaxation and sedation (15). If the patient's sedation was insufficient, the patient received intravenous midazolam at a dose of 1.5 mg. The data were processed using SPSS software version 22, applying descriptive statistics (frequency, percentage, mean, and standard deviation) and inferential statistical tests (t-test) to determine significant differences at a P-value of < 0.05.

Results

This study examined a total of 89 patients, with the majority being male, and no significant difference in gender distribution was found between the intervention and control groups ($P = 0.83$). The need for morphine was significantly lower in the intervention group, with none of the patients requiring morphine, compared to 63.64% of the control group ($P < 0.001$). The average pain scores were significantly lower in the intervention group at all time points, including 1 hour (2.51 ± 0.59 vs 4.00 ± 0.62), 6 hours (3.56 ± 0.73 vs 5.75 ± 0.69), 12 hours (3.27 ± 0.94 vs 5.32 ± 0.80), and 24 hours (4.36 ± 1.09 vs 6.00 ± 0.61), with P-values < 0.001 for all time points. Similarly, the average RASS scores were also significantly lower in the intervention group at all time points, including 1 hour (-1.24 ± 0.61 vs 0.57 ± 0.587), 6 hours (-0.58 ± 0.58 vs 1.50 ± 0.550), 12 hours (-1.20 ± 0.69 vs 0.61 ± 0.538), and 24 hours (-0.11 ± 0.32 vs 1.70 ± 0.462), with P-values < 0.001 for all time points. These results suggest that the intervention was effective in reducing the need for morphine, pain scores, and RASS scores compared to the control group.

Discussion

Postoperative pain is a prevalent and debilitating complication that can lead to a range of negative outcomes, including prolonged recovery, increased morbidity, and prolong hospital stays (16-17). Usually, the highest pain intensity (NRS) is experienced in the first days after surgery, so that in these few days, patients mainly need strong pain relievers such as intravenous or oral opioid compounds (18-24). Although analgesics like cyclooxygenase inhibitors or prostaglandin inhibitors and narcotic agonists are commonly administered to alleviate nociceptive and

neuropathic pain, they have harmful side effects such as gastrointestinal problems, postoperative drowsiness, nausea and vomiting, respiratory depression, and bladder dysfunction in the short term. The duration and risk of addiction are also long-term (25). Therefore, in order to alleviate these complications, this investigation pointed out effects of adding intravenous ketamine to methadone in controlling the pain of opium-addicted patients after major surgery in the special care department of Bandar Abbas Shahid Mohammadi Hospital. 89 opium-addicted patients aged 18 to 75 years with ASA class 1 or 2 who underwent major elective surgery were included in the study. The studied groups were similar in terms of demographic characteristics.

Examining the frequency of need for morphine and postoperative pain in two intervention and control groups shows that the majority of patients in the control group (63.64%) needed morphine, while the need for morphine was negative in the intervention group. The results of the chi-score test showed that there is a significant difference between the intervention and control groups in terms of the need for morphine. On the other hand, there was a significant difference in the average pain between the intervention and control groups at the first postoperative day. The average pain at the first postoperative day was lower in intervention group than the controls. Some studies have investigated the effectiveness of ketamine and methadone on postoperative pain and the need for narcotics caused by it. Khalili et al. (2018) investigation in laparoscopic cholecystectomy surgery with similar study arms to our study found same results. Nonetheless, the analysis showed no significant variation in the requirement for painkillers across the groups being studied (26). This study is different from the current study due to the non-significance of the need for morphine, which can be attributed to the simultaneous use of ketamine and methadone in the current study compared to this study. Researchers explored the synergistic pain-relieving effects of a dual-agent regimen comprising methadone and ketamine in spinal surgery patients, revealing that this combination therapy significantly enhanced postoperative analgesia, modulated NMDA and opioid receptors, and subsequently decreased the requirement for supplementary opioid medications, thereby demonstrating its efficacy in mitigating severe postoperative pain and analgesic consumption (27). In their study, Park et al. (2012) examined the effectiveness of methadone plus ketamine regimen on opioid consumption in comparison of the standard care regimen. Postoperatively, ketamine led to 70-80% lowered narcotic usage. Therefore, the combination of ketamine-methadone significantly reduces the consumption of opioids after surgery (28). This study, similar to the current study, shows the effectiveness of the combination of ketamine-methadone in reducing pain and the need for opioids after surgery.

Park et al.'s (2020) review showed that Ketamine's postoperative analgesic efficacy was assessed in 10 studies, revealing 7 showed reduced opioid use, while 3 showed no difference (29). Most of the studies reviewed in this systematic review are similar to the present study. To check the effectiveness of these two drugs more precisely, it is necessary to know the pharmacology and pharmacokinetic characteristics of these two drugs.

Methadone cannot be the drug of choice for a patient with an acute illness whose hospitalization period is changing rapidly. Methadone can be a good choice for patients who have a long recovery period ahead and also for patients who are expected to be separated from the ventilator for a long time (30-34). Often, when patients' clinical conditions are stabilized, switching from fentanyl or morphine infusion to methadone intramuscularly can help simplify care plans and reduce infusion dependence (34). Ketamine is a derivative of phencyclidine, and one of its features is non-suppression of the cardiovascular system and a strong analgesic effect. Administering a dose lower than the anesthetic amount (subanesthetic) of ketamine before induction of

anesthesia provides adequate analgesia, which prevents severe hemodynamic changes and does not have a bad effect on the patient's breathing (36-39), such as methadone and ketamine. Therefore, according to the studies and characteristics mentioned for each of these drugs, it is clearly visible that the combination of these two drugs with each other by creating a synergistic property plays an important and significant role in reducing pain and the need for narcotics after surgery. It plays a role in patients, especially drug addicts. In our study, Intervention group had lower RAAS and sedation needs at all times.

Previous reviews and meta-analyses have shown that adverse outcomes occur in patients receiving methadone (40) or ketamine (41). Even low-dose ketamine was noninferior to methadone for postoperative pain in opioid addicts. Based on the reported results, central nervous system complications (sedation, hallucinations and vertigo) were few and no significant difference was observed between patients in the ketamine and methadone groups (42). All these studies have reported the limited side effects of the nervous system caused by the use of ketamine and methadone, but in the present studies, the results show that the combination of ketamine and methadone can significantly reduce restlessness in drug users and decrease the requirement for sedative medication in this patient population

Commonly, a range of adverse reactions may arise when methadone or ketamine are administered during the post-surgical period, encompassing stomach upset and vomiting, slowed breathing, drowsiness, skin itchiness, rapid heartbeat, high blood pressure, and intense visual disturbances (43-46). A study conducted by Murphy et al. (2021) explored the combined use of ketamine and methadone in the post-surgical timeframe and found that the occurrence of adverse reactions related to the respiratory system (low oxygen levels, shallow breathing), central nervous system (drowsiness, vivid dreams, dizziness) and gastrointestinal system (stomach upset, vomiting) was relatively low, with no notable discrepancies observed between the study groups. Furthermore, the overall rate of complications throughout the hospital stay was comparable between the two groups, with no significant differences detected (27). Similarly, a study by Khalili et al. (2018) reported no substantial differences among the ketamine, methadone, and control groups in terms of changes in blood pressure and post-surgical complications (26).

Conclusion

The results of the present study show that adding intravenous ketamine to methadone controls pain and reduces the need for morphine in opium-addicted patients after major surgery in the intensive care unit without serious side effects. Therefore, this combination can be used in this group of patients to reduce pain and reduce recovery time.

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Authors Contributions:

All authors conceptualized the study objectives and design.

Ethical Consideration:

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Tables:

Table 1: Demographics and outcomes of intervention and control groups

Variable	Intervention	Control	P-value
Male Sex	81.82% (36)	80% (36)	0.83
Need for Morphine (Yes)	0% (0)	63.64% (28)	<0.001
Pain (1 hour)	2.51 ± 0.59	4.00 ± 0.62	<0.001
Pain (6 hours)	3.56 ± 0.73	5.75 ± 0.69	<0.001
Pain (12 hours)	3.27 ± 0.94	5.32 ± 0.80	<0.001
Pain (24 hours)	4.36 ± 1.09	6.00 ± 0.61	<0.001
RAAS (1 hour)	-1.24 ± 0.61	0.57 ± 0.587	<0.001
RAAS (6 hours)	-0.58 ± 0.58	1.50 ± 0.550	<0.001
RAAS (12 hours)	-1.20 ± 0.69	0.61 ± 0.538	<0.001
RAAS (24 hours)	-0.11 ± 0.32	1.70 ± 0.462	<0.001