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Comparative efficacy of ketamine, lidocaine, acetaminophen, and dexmedetomidine combined with morphine patient-controlled analgesia in treating opium-addicted patients undergoing tibia fracture surgery: A randomized clinical trial

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ABSTRACT

Objective: To compare the effect of ketamine, lidocaine, acetaminophen, and dexmedetomidine combined with morphine patient-controlled analgesia for opium addicts after tibial fracture surgery.

Methods: This double-blind clinical trial included opium-addicted patients undergoing tibia fracture surgery. Patients were recruited and randomized to four different groups including the ketamine group, the lidocaine group, the acetaminophen group, and the dexmedetomidine group. The hemodynamic parameters such as heart rate (HR), mean arterial pressure, and arterial SaO_2, alongside visual analog scale pain scores, sedation assessed by Ramsay score, nausea and vomiting, and opioid use were recorded and compared among the four groups.

Results: This study included 140 patients, aged 37 (32, 41) years, with 92 males and 48 females, and each group had 35 patients. Dexmedetomidine-sedated subjects had the lowest blood pressure from 1 to 24 h after surgery, decreased HR at 12 and 24 h after surgery, and more satisfactory sedation (P<0.05). Notwithstanding no significant difference was noted in the pain scores, or nausea and vomiting among the groups (P>0.05).

Conclusions: Dexmedetomidine has a better sedation effect compared to ketamine, lidocaine, and acetaminophen for pain control, but the final choice hinges on the patients' physical condition and the anesthesiologist's preference.

Clinical registration: It is registered in Iranian Registry Clinical Trial by code IRCT20141209020258N146.

KEYWORDS: Acetaminophen; Dexmedetomidine; Ketamine; Lidocaine; Morphine; Opium-addicted patients; Tibia fracture surgery; Patient-controlled analgesia pump; Postoperative pain

Significance

Dexmedetomidine is preferable in comparison to ketamine, lidocaine, and acetaminophen when combined with morphine in patient-controlled analgesia for opium-addicted patients by increasing sedation, lowering complications, and preventing postoperative agitation. Thereby, dexmedetomidine is recommended when higher analgesia and sedation are considered, while in management of postoperative pain, all four drugs could be used for opium-addicted patients.

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1. Introduction

Modern medicine still could not successfully prevent a wealth of patients from experiencing relatively severe pain following major surgery[1]. Opioids are believed to be highly commonly administered drugs to alleviate postoperative pain and usually used for intravenous patient-controlled analgesia (PCA) (*i.v.*)[2]. Morphine, an opium-derived analgesic, is a greatly potent opioid and the most powerful active analgesic naturally found in opium[2,3]. Its analgesic efficacy is mediated by binding to the opioid receptors widely distributed throughout the brain, including the thalamus, brainstem, and spinal cord, while found along the pain pathway[4]. Tolerance to analgesic actions may be the reason why postoperative pain management remains controversial for patients taking long-term opioids[5].

Literature shows that cellular mechanisms of tolerance to morphine include the increase or decrease in opioid receptors, the changes in intracellular transmitters such as adenylyl cyclase, protein kinase C, and the interference of post-synaptic receptors, particularly glutamate/aspartate receptors, γ-aminobutyric acid, and monoamine neurotransmitters inside central serotonergic nerves[6]. It is also reported that combined drugs could enhance efficacy in treating patients with a history of addiction to opioids[7,8].

Ketamine applies its analgesic effect *via* non-competitive inhibition of *N*-methyl-*D*-aspartate receptor[9,10]. Furthermore, plenty of studies have documented the analgesic effect of ketamine combined with opioids such as pethidine[7] and methadone[8].

Dexmedetomidine, an active enantiomer of medetomidine, is known as a highly selective α2-adrenergic agonist and an imidazole derivate, showing a sedative effect different from other *i.v.* anesthetics. It could further induce physiological sleep and act through endogenous sleep pathways. Stimulation of α2-adrenergic receptors may help improve postoperative pain[11]. Dexmedetomidine, as Anderson *et al*. reported, provides a more effective analgesic effect during the postoperative period and prolonged duration of sensory and motor block with minimal side effects[12]. Furthermore, Lin *et al*. concluded that adding dexmedetomidine to morphine PCA can decrease nausea and vomiting and improve sedation scores[13].

Lidocaine is regarded as a local anesthetic, works by inhibiting calcium channel function, and exerts obvious analgesic and anesthetic effects by *i.v*. administering and local injections[12]. Evidence has supported that *i.v*. lidocaine injection could reduce postoperative pain and opioid use and improve postoperative rehabilitation[13,14]. Lidocaine *i.v*. has analgesic, antihyperalgesic, and anti-inflammatory properties. The latter property can reduce postoperative inflammatory response by blocking neural transmission at the site of tissue injury, thus attenuating postoperative neurogenic inflammation[13-15].

Nonsteroidal anti-inflammatory drugs are another common class of analgesics used in some studies. Acetaminophen or *N*-acetyl-para-aminophenol has been administered for postoperative pain management[16,17]. More recently, a combination of nonsteroidal anti-inflammatory drugs with *N*-acetyl-para-aminophenol has shown promise for managing acute postoperative pain[11].

It is important to study postoperative pain and tolerance of morphine-addicted patients. There is a lack of studies comparing the efficacy of ketamine, dexmedetomidine, lidocaine, and acetaminophen combined with morphine in treating opioid-addicted patients after tibia fracture surgery. This study aimed to identify and introduce the best analgesic combination with the least side effects.

2. Patients and methods

2.1. Study setting

The double-blind clinical trial enrolled opium-addicted patients undergoing tibia fracture surgery from July 2020 to March 2021.

2.2. Inclusion and exclusion criteria

Inclusion criteria included (1) patients aged 20 to 60 years; (2) the American Society of Anesthesiologists class I and II; (3) no obesity (body mass index <30 kg/m^2); (4) no chronic pain; (5) no mental disorders; (6) no history of seizures; (7) no use of psychotropic drugs; (8) no daily use of painkillers more than once a week; (9) lack of sensitivity to drugs; (10) no upper respiratory infection; (11) no pregnancy and lactation; (12) no history of postoperative nausea and vomiting; (13) no cardiovascular disease; 14) no hemodynamic instability.

Patients dissatisfied with participation, lack of cooperation, and refusing spinal anesthesia were also excluded.

2.3. Intervention

Participants were randomly divided into four groups using block randomization with randomly selected block sizes of 4 and 8 and the daily use of opium during the examination one night before surgery was recorded.

All patients received 10 mg *i.v.* morphine at a specific hour of the day before surgery to prevent withdrawal symptoms. At the beginning of entering the operating room, each patient received 10 mL/kg of Ringer's solution and then vital signs were controlled and recorded. The spinal anesthesia was performed with a 25-gauge Quincke needle in the midline at the L3-L4 or L4-L5 interspace. All patients were injected intrathecally with bupivacaine 15 mg to induce anesthesia and then with 2 mg midazolam after spinal anesthesia for sedation during surgery. Throughout the surgery, heart rate (HR), mean arterial pressure, and arterial SaO_2 were monitored for the first 15 min every 5 and then 15 min until the end of the surgery and in the recovery room at 1, 6, 12, and 24 h postoperatively.

Hypotension was defined as a decrease in systolic pressure to 20% below baseline, bradycardia as HR<45 bpm, and hypoxemia as

SaO_2<92%. If stable, any appropriate remedial action was performed and recorded, whereas patients received ephedrine 5 mg for hypotension, atropine 0.5 mg for bradycardia, and 4 L/min of oxygen *via* nasal cannula for SaO_2 <92%[12]. After the surgery, the patient was transferred to recovery, and PCA was connected immediately.

Ketamine group: Ketamine 1 mg/kg added to morphine PCA[18] (Ketamine 50 mg/mL vial, Rotexmedica, Germany).

Acetaminophen group: *N*-acetyl-para-aminophenol 15 mg/kg added to morphine PCA[19] (Acetaminophen or paracetamol, 1 000 mg, 150 mg/mL, 6.7 mL vial, Cobel Darou, Iran).

Lidocaine group: Lidocaine 1.5 mg/kg added to morphine PCA[20] (Lidocaine, 2%, 5 mL vial, Caspian Tamin, Rasht, Iran).

Dexmedetomidine group: Dexmedetomidine 1 μg/kg added to morphine PCA[13] [Dexmedetomidine 200 mg (100 mg/mL) vial, Exir Pharmaceutical Co, Iran].

The volume of the basic drug (20 mg morphine) was diluted to 86 mL with normal saline in all groups and then the intervention drug dose, when calculated, was diluted to 10 mL with normal saline and loaded into the PCA. Hence, the total volume of each PCA pump was 96 mL. The injection speed was set at 4 mL/h, based on the fact that each PCA pump was intended for 24 h. Patients were visited at specific times during 24 h, whereas pain, sedation, nausea and vomiting scores were recorded. After 24 h, PCA was removed from the patient. Patients' pain score was measured with visual analogue scale on a 0-10 scale, where 0 indicates the absence of pain and 10, the most severe pain.

Sedation level was assessed by Ramsay score scale, where 1 refers to anxious and agitated, 2 awake and cooperative, 3 asleep, awakened by calling, 4 sleeping deeply, awakened by painful stimuli, 5 sleeping deeply, responded slightly to painful stimuli, 6 responded to stimuli and deeply sedated. The severity of nausea and vomiting was scored using nausea vomiting scale where, 0 refers to no complaints, 1 mild nausea, and 4 severe vomiting. Nausea, vomiting, pain, and sedation scores, as well as vital signs, were recorded at 1, 6, 12, and 24 h after PCA was started. If visual analogue scale ≥4, 2.5 mg morphine was injected intravenously, while the time was recorded. It is remarkable to note that all data were measured and recorded by an intern, unaware of the group allocation to ensure a double-blind study design. The drugs were prepared in each group by an anesthesiologist.

2.4. Ethical statement

All patients and their parents were informed about the objectives of the study and signed the written informed consent. This study is approved by Ethical Committee of Medical University by IR.ARAKMU.REC.1399.060 code and its protocol is registered in Iranian Registry Clinical Trial by code IRCT20141209020258N146.

2.5. Endpoints

The primary outcomes of our study were hemodynamic parameters. In addition, the pain score, Ramsay score, nausea and vomiting occurrence were secondary outcomes.

2.6. Statistical analysis

Sample size calculation and the required sample for each study group were calculated using the results of our recent study[21] and considering the study power being equal to 80% as well as the confidence interval of 95% in each group equaling 33 patients.

Data were analyzed by SPSS 20. Descriptive data were expressed by frequency and percentage and numerical data were expressed by mean±SD or median (Q1, Q3). whereas *Chi*-square and ANOVA statistical tests or Kruskal-Wallis test were used to compare the four groups. The significant level of this study was set at α=0.05.

3. Results

This double-blind trial enrolled 140 patients scheduled for orthopedic surgery, who were randomized into four groups (Figure 1). The age was 37 (32, 41) years. The mean body mass index was (23.51±2.89) kg/m^2, and 92 (65.7%) were men and 48 (34.3%) women. No statistically significant difference was seen in SaO_2, duration of surgery, pain, the total amount of opioid use, and nausea

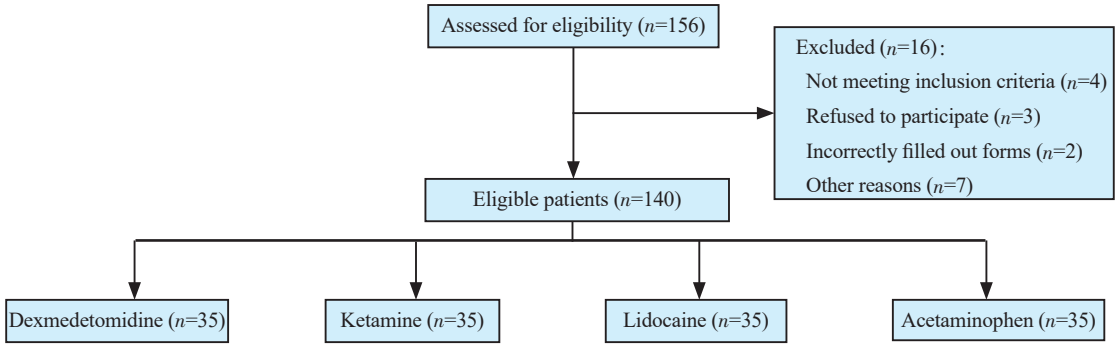

Figure 1. The study flowchart.

Table 1. Patient characteristics of the four groups.

Parameters	Ketamine, *n*=35	Acetaminophen, *n*=35	Lidocaine, *n*=35	Dexmedetomidine, *n*=35	*F*/ χ^2/*H*	*P*
Age, year, mean±SD	37.26±7.57	36.91±7.34	37.02±7.80	37.77±7.81	0.087	0.967
Sex (male), *n*, %	24 (68.4)	23 (65.7)	22 (62.9)	22 (62.9)	0.345	0.951
BMI, kg/m^2, mean±SD	23.17±2.83	23.40±2.82	23.51±2.89	23.97±3.10	0.466	0.706
SaO_2, %, mean±SD	96.60±0.81	96.74±0.88	96.57±0.88	96.54±0.74	0.398	0.755
Duration of surgery, min, mean±SD	102.37±6.02	102.91±5.59	102.37±5.97	102.37±6.09	0.073	0.974
VAS score, mean±SD	2.28±0.45	2.29±0.43	2.31±0.47	2.25±0.44	0.091	0.965
Amount of opioid use, mg, median (Q1, Q3)	2.00 (1.00, 3.50)	2.25 (1.00, 3.75)	2.70 (1.45, 4.30)	2.15 (1.90, 3.15)	0.952	0.325
Nausea and vomiting complications, *n*, %	4 (11.4)	6 (17.1)	7 (20)	1 (2.9)	5.350	0.148

BMI: Body mass index; VAS: Visual analog scale.

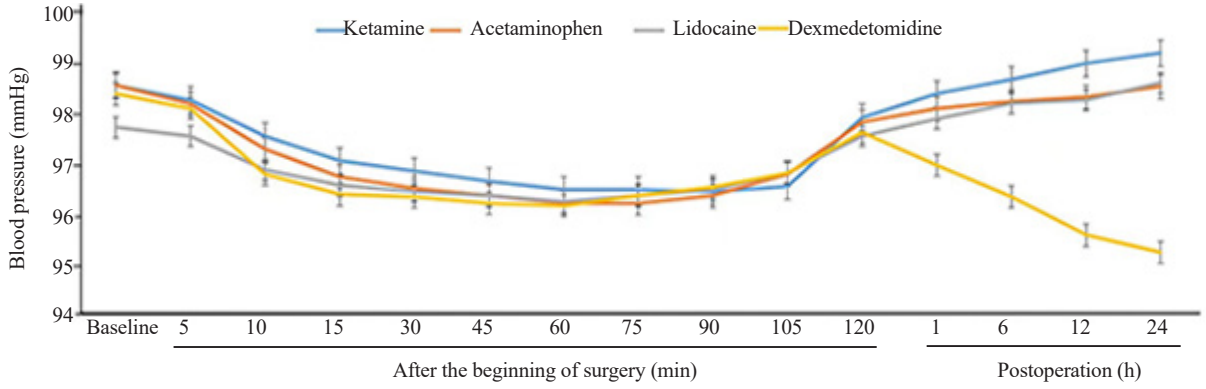

Figure 2. Blood pressure in the four groups.

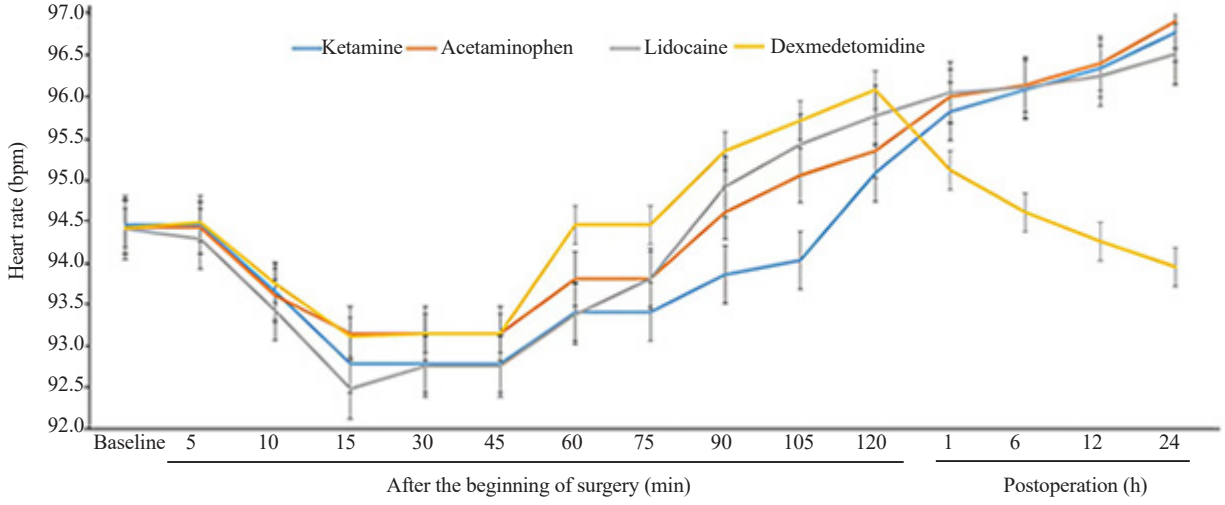

Figure 3. Heart rate in the four groups.

and vomiting among the four groups (P>0.05), and they were similar in age, sex and boday mass index (P>0.05) (Table 1).

There was no significant difference in mean blood pressure (BP) among the four groups at the baseline to 120 min after the surgery (P>0.05), while a statistically significant difference was observed in BP from 1 to 24 h after operation (P<0.05), which was lower in the dexmedetomidine group (Figure 2).

As the results in Figure 3, four groups were similar regarding the mean of HR from the starting surgery to 6 h after surgery (P>0.05). Nevertheless, a statistically significant difference was observed in HR at 12 and 24 h after operation (P<0.05), which was slower in the dexmedetomidine group.

Based on the results, a statistically significant difference was observed in sedation among the four groups (P<0.05) and it was higher in the dexmedetomidine group (P=0.001)(Figure 4).

4. Discussion

This double-blind clinical trial enrolled 140 patients undergoing orthopedic surgery at the Arak Valiasr Hospital, who were randomly divided into four groups of dexmedetomidine, acetaminophen, ketamine, and lidocaine, among which no statistically significant difference was found in SaO_2, duration of surgery, pain, the total

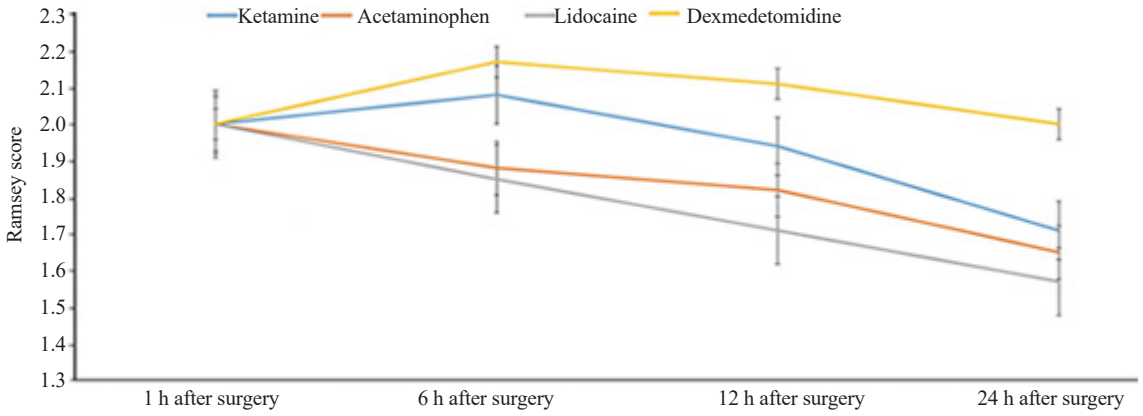

Figure 4. Changes in Ramsey score in the four groups .

amount of opioid use, or the incidence of nausea and vomiting (P<0.05). The dexmedetomidine group manifested the lowest BP from 1 to 24 h after operation (P<0.05) and decreased HR at 12 and 24 h postoperatively, while sedation score was higher in the dexmedetomidine group (all P<0.05). Overall, dexmedetomidine could provide better sedation and reduce HR and BP postoperation. Dexmedetomidine is described as the active enantiomer of medetomidine and is a highly selective α2-adrenergic agonist and an imidazole derivate. The sedative effect of dexmedetomidine is different from that of other *i.v.* anesthetics. It is more similar to physiological sleep and acts through endogenous sleep pathways[11]. Najafi *et al.*'s study on the effect of adding ketamine to morphine in opioid-addicted patients after orthopedic surgery suggested that the addition could reduce morphine use but does not reduce pain and sedation score[18], while all drugs used in our study caused nausea and vomiting and dexmedetomidine was more effective. Habibi *et al.* assessed the effect of adding lidocaine to morphine PCA on pain intensity after cesarean section with spinal anesthesia and demonstrated that the intensity was significantly reduced in the first 24 h postoperation and that generally no significant difference was found in pain intensity in the first 24 h postoperation between the two groups at any time[19].

Peng *et al.* evaluated the effects of dexmedetomidine combined with opioids on postoperative pain management. Their review study included 7 randomized controlled trials in which combined opioid-dexmedetomidine PCA was studied for 24 h. Pain was relieved, nausea and vomiting were reduced, and patients' satisfaction was improved when they used a mixture of dexmedetomidine and opioids. They concluded that the mixture is safe and effective in managing patients' pain[20], whereas those results were in the same line as ours.

Hashemi *et al.* undertook a study to compare effect of *i.v.* paracetamol and morphine on trauma patients after arthroscopy. Although no difference was observed in pain between the two groups, 22.3% of patients who received morphine suffered from nausea and vomiting. However, they were not different in terms of sedation level, nausea and vomiting. They reported that *i.v.* paracetamol injection immediately after knee arthroscopy can improve postoperative pain, maintain hemodynamic parameters, reduce nausea and vomiting, and improve patient satisfaction and comfort compared to morphine PCA[21]. Furthermore, our study showed that nausea and vomiting were alleviated, opioid use and pain were reduced in all groups, while dexmedetomidine was more effective.

Alimian *et al.* explored the effect of adding paracetamol to morphine PCA after elective laparotomy and recruited 150 patients in the study. The first and second groups received 4 g paracetamol and 20 mg morphine PCA, respectively within 24 h. A significant difference in pain scores was found in the first 8 h but not 12 h after the operation. Similarly, no difference was observed in nausea and vomiting between the two groups. Paracetamol was considered to relieve pain and could reduce opioid need for pain management during the first 8 h[22].

Alebouyeh *et al.*'s study evaluated the analgesic effects of adding lidocaine to morphine PCA in orthopedic surgery. While pain score and opioid use were lower in the first group, nausea and vomiting were not different. Lidocaine 1% plus 20 mg morphine further reduced pain and opioid use decreased 24 h after operation, while no drug side effects were observed[23]. All drugs used in our study increased sedation, while dexmedetomidine was more effective.

Similarly, Lin *et al.*'s study aimed at comparing the effect of combining dexmedetomidine and morphine for *i.v.* PCA and recruited 100 women undergoing hysterectomy, where the first group received 1 mg/mL morphine while the second, 1 mg/mL morphine plus 5 μg/mL dexmedetomidine. The latter group had less pain but reduced HR and BP, whereas nausea and vomiting were lower in the group. They concluded that adding dexmedetomidine to morphine PCA could reduce nausea and vomiting and improve patients' sedation level[13]. Though the results were similar to our study, the highest incidence of nausea and vomiting were observed

in lidocaine, acetaminophen, and ketamine groups, respectively, but better sedation was seen in the dexmedetomidine group.

In Burstal *et al*.'s study on the effect of ketamine and morphine PCA after abdominal hysterectomy, the morphine group received 1 mg/mL morphine and the ketamine group, 1 mg/mL morphine plus 2 mg/mL ketamine. Adverse effects, *i.e.* nausea and vomiting were worse in the latter group. The potential efficacy of ketamine after hysterectomy is offset by the high incidence of adverse effects and a lack of opioid-sparing effects, therefore, combination of *i.v.* ketamine and morphine PCA usage may not be recommended for routine care[24]. Since four patients in our ketamine group had postoperative nausea and vomiting, their results were consistent with ours.

This study compared four different common adjuvants combined with morphine patient-controlled analgesia for opium-addicted patients and showed that dexmedetomidine has the most significant effect on sedation and hemodynamic parameters. Nevertheless, follow-up of patients after hospital discharge for future complications did not conduct and the absence of a control group make the conclusion difficult for comparing ketamine, and lidocaine, acetaminophen adjuvants.

Based on the results of the study, dexmedetomidine is preferable to other drugs due to increasing sedation and preventing postoperative agitation, but no significant difference was noted in terms of postoperative pain management among the groups. Dexmedetomidine is recommended when higher analgesia and sedation are considered, while if the goal is merely to manage postoperative pain, all drugs used in this study can be administered for opium-addicted patients, and the final choice depends upon the patient's physical condition and the anesthesiologist's preference.

Conflict of interest statement

The authors report no conflict of interest.

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Authors' contributions

H.M.: Contributions to the conception or design of the interpretation of data for the work and final approval of the article; E.M.: Contributions to the conception or design of the interpretation of data for the work and final approval of the article; M.A.: Contributions to the conception or design of the work and final approval of the articles; M.J.Z.: Contributions the acquisition and analysis of data for the work and drafting the article; A.A.H.: Contributions the acquisition and analysis of data for the work and drafting the article.

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