

Efficacy of dexmedetomidine and ketamine addition to bupivacaine 0.25% by epidural method in reducing postoperative pain in patients undergoing femur fracture surgery

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ABSTRACT

Background and Aim: One of the most complex medical problems is pain, that due to inappropriate management of patients after surgery could cause various side effects on the psychological, physiological, and metabolic state of the patients. The natural duration of analgesia can be increased by adding new efficient adjuvant. The present study is mainly aimed to investigate the differences between the epidural dexmedetomidine and ketamine effectiveness when administered as an adjuvant to epidural 0.25% bupivacaine for improving the postoperative analgesia duration. **Methods:** In the present double-blind clinical study, 105 patients of the age range of 40-85 years were selected for elective femoral surgery and then was divided into three of ketamine, dexmedetomidine, and control randomly. The scores of postoperative pain were evaluated in accordance with the visual Analogue Scale (VAS) criteria and the duration of analgesia and the amount of analgesics consumption were recorded. **Results:** The mean pain VAS score during the first day after the surgery and recovery of patients in the dexmedetomidine group was significantly lower in comparison with two other groups ($p = 0.01$). However, no significant difference was found in the mean VAS score of Pain during 12 and 24 hours after the operation ($P \geq 0.05$). Comparisons among these groups demonstrated that the mean on opioid administration during the operation and 24 hours after that was significantly higher in both groups of ketamine and control in comparison with the dexmedetomidine group ($P = 0.001$ and $P = 0.01$). Besides, analgesia duration among patients belonged to the dexmedetomidine group was notably lower in comparison with two other groups ($P = 0.001$). **Conclusion:** In epidural anesthesia cases adding ketamine and dexmedetomidine as adjuvants to the solution of bupivacaine 0.25%, could increase the duration of analgesia and reduce the consumption of analgesics, which is more in the dexmedetomidine group when compared with ketamine.

Keywords: Dexmedetomidine, epidural anesthesia, femoral fracture, ketamine, postoperative pain

Introduction

One of the most prevalent health issues is bone fractures treatment that femoral fractures are among the most prevalent

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ones. These types of fractures are usually found in young and active people, usually caused by work-related accidents and driving-induced traumas, while older people encounter such fractures due to physiological conditions and decreased bone density.^[1] Nearly all fractures related to the femoral bone need internal fixation that is managed by surgery; from another point of view, it is very easy and understandable that both pain and pain intensity are significantly higher in these patients, and naturally

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pain complications are also more.^[2] these patients have a range of medical problems, these conditions require special considerations for anesthesiologist, which has led to the evaluation of various anesthetic techniques. As a result, regional techniques are of particular importance, of which epidural anesthesia can bring multiple goals to these patients.^[3] Also, epidural anesthesia reduces the complications during the operation.^[4] An increasing body of evidence indicates that benefits of postoperative epidural analgesia can make patients more comfortable and improve their quality of life.^[5]

One of the important advantages of regional anesthesia alone or in combination with general anesthesia is to relieve pain without the need for narcotics during the postoperative period, where this advantage results in quicker movement and a shorter hospitalization time. Postoperative pain can lead to changes in the neuroendocrine system by producing a stress response that causes a hypermetabolic and catabolic state in the patient, leading to imbalance in water, electrolytes, macronutrients and micronutrients and worst conditions in the patient undergoing stressful surgery.^[6,7] In addition, postoperative pain increases the potential for complications such as increased coagulation, immobility, DVT, pulmonary embolism, myocardial ischemia, immune suppression, impaired wound healing and ileus, where is capable of showing a significant effect on motility and morbidity during surgery.^[8] A large-scale research on drug alternatives for the main neuromuscular and adjuvant anesthetic has been undertaken.^[9] These adjuvants have been used in combination with topical anesthetics to improve analgesia and reduce complications, however, none of them have been found to be acceptable.^[10] Ketamine and dexmedetomidine are among the most appropriate drugs that are introduced recently presented as adjuvant drugs but in spite of their introduced theoretical effects, just little clinical studies have been done about them.^[11] Dexmedetomidine is a selective agonist of α -2 adrenergic receptors, which exhibit a sleeping and analgesic effect. A study conducted by Kamali *et al.*^[12] demonstrated that the combination of 0.25% bupivacaine with perineural dexmedetomidine could cause a non-neurotoxic blockade of the motor and sensory functions. Other adjuvant drugs include ketamine, as an NMDA receptor inhibitor that is now increasingly used for postoperative pain control. The remedial effectiveness of ketamine is mainly because of its antagonistic characteristics on N-methyl-D-aspartate (NMDA) receptors that indicates its remedial efficiency in modifying resistance to opioids.^[13]

Consequently, the main objective of the present study is investigating the effectiveness of ketamine, and dexmedetomidine as adjuvant drugs in company with bupivacaine for activ surgical procedures in femoral fractures.

Material and Methods

Study design

The present study as a double-blind clinical trial was conducted on patients referred to Hospitals of Arak who had femoral bone

fractures and then were candidates for surgery. After that, patients were chosen randomly then after completing a full description of the patient's condition and intervention, through obtaining written consent from the patients, they were included in the study. In this study, 105 patients with femoral fractures based on the inclusion criteria were randomly divided into three groups of dexmedetomidine, ketamine and placebo, in which 35 patients were assigned to each group [Figure 1]. Study was performed between 11th February and 11th November 2019.

In all stages of the research, the principles of the Medical Ethics Committee of Arak University of Medical Sciences were considered. Study mode and conditions of participation in the study were described for patients. Written consent was also obtained from patients.

Inclusion and exclusion criteria

Inclusion criteria included: Having informed consent, Patients aged 40–85 years, Patients with American Society of Anesthesiologists (ASA) Class II and I, Lack of anaphylaxis, no substance misuse, no contraindication for epidural analogy, Duration of surgery between 120 and 90 minutes, all patients undergo surgery.

Exclusion criteria included: Patients outside the age range of 80-40 years: Patients with grade III ASA and IV: Patients with substance abuse: patients with BMI \geq 35, Epidural anesthesia in patient with fracture, undergoing general anesthesia, Patients with underlying ischemic heart disease (IHD), Diabetes. rheumatoid arthritis (RA), asthma, etc.

Method description

All patients received a crystalloid fluid of 3-5 cc/kg as CVE 10 to 15 minutes before operation; after entering the operating room complete monitoring was performed for all patients. BP, PR, and SPO2 were recorded in the questionnaire. Moreover, all patients were then placed under an epidural nerve block procedure in a sitting position (in the L3–4 or L4–5) through needle 21-20 (BiBron, Germany) using the loss of resistant. (CVE:

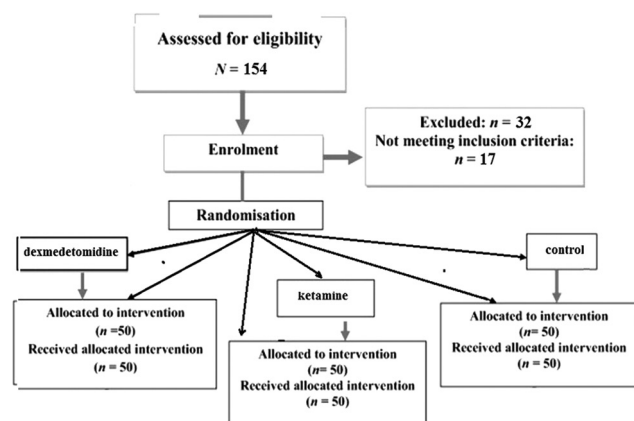


Figure 1: CONSORT Flow Diagram

Compensatory intravascular volume expansion) Then, Epidural catheter was fixed for patients. Depending on the dermatomes involved, marcaine 0.25% in dose of 2 cc/segment (about 18-18 cc) was injected into the epidural space for analgesia.

All the studied groups received an equal amount of bupivacaine 0.25% solution in a dosage of 2 cc/segment. Additionally, a loading dose of 0.5 µg/kg (30-35 mg) of dexmedetomidine was used, while the second group received 25 mg of ketamine (equivalent to 0.5 cc) and the same normal saline (0.5 cc) was given to the control group. Aiming to increase the final solution volume to 20 ccs, saline was applied for all of the studied groups. In order to regard Blindness, the drugs were prepared by the anesthetist responsible for the design, and then given to the resident responsible for the project to be injected into the epidural space. Afterward, patients were immediately admitted to the supine position and V/S of patients was next recorded. For compensation of the liquids that patients have lost during the operation, the ringer solution was administered. In the present study, the exclusion criteria were patients who experienced severe bleeding, patients whose operation time was more than two hours, patients who need blood transfusion due to severe bleeding, and patients whose epidural anesthesia failed.

At the time of neural blockade, the score of pain for each patient was recorded using a visual analog scale (VAS). The administered visual analog score system was ranging from zero (no pain) to 10 cm (intolerable pain) at the post-anesthesia care unit (PACU) at different time intervals of 6, 12, and 24 hours following the surgical operation. When the pain score was 3 or more, 30 mg of pentazocine was administered through intramuscular injection. On the other hand, when the management of pain is poor, after one hour 25 mg of pentazocine should be administered. In two of the studied pain scores, the amount of pentazocine used for each patient, pentazocine side effects, vomiting, nausea, itching, and any available complication was recorded.

It is worth noting that V/S patients were recorded in the patients' questionnaire every 5 min to 15 min and 15 min to 15 hl, after entering the recovery. Furthermore, scores of patients' pain was recorded through the VAS ruler in the patients' questionnaires. In addition, a range of measurements were also recorded including pain duration, pain scores postoperative, and the mean of opioid use at 24 h after surgery. All relevant information was recorded and evaluated by a physician.

Ethical consideration

This research was approved with the code of ethics IR.ARAK.MUREC.1395.210 in September 2016, and also the registration code in the clinical trial center is IRCT2016102620258N16.

Statistical analysis

Statistical analysis of the data was carried out by SPSS software. Furthermore, ANOVA and T-test were used for analyzing the obtained data from the present study.

Results

In this study, a total of 105 patients with femoral fractures were divided into three groups randomly that include dexmedetomidine, ketamine and placebo, in which 35 patients were assigned to each group. The data achieved from the statistical analysis of the present study in terms of sexual frequency and mean age did not show a significant difference between the three studied groups. Based on the data presented in Table 1, in all groups, the mean age and the frequency of females were 74 years and 64%, respectively.

Assessment of pain scores during the recovery and four hours after the operation demonstrated that there wasn't any significant association among them. It's while the pain score in the dexmedetomidine group at these times was lower in comparison with two other groups ($P = 0.01$). Anyway, there weren't any significant differences in mean pain scores between the three studied groups following 12 and 24 hours after the operation ($P \geq 0.05$), [Table 2].

The finding of the present study demonstrated that there was a significant difference between the three studied groups in terms of opioids consumption during the operation and 24 hours after operation, so that the average drug use in the dexmedetomidine group was low in comparison with two other groups during the operation and 24 hours after the operation ($P = 0.001$; $P = 0.01$), [Table 3].

The three groups did not show a significant difference in the duration of postoperative analgesia. Based on the data from Table 4, while the duration of postoperative analgesia in the dexmedetomidine group was higher in comparison with the other two groups ($P = 0.001$), the duration of analgesia among ketamine and placebo groups was the same.

During the recovery time, the incidence rate of shivering in the dexmedetomidine group was approximately zero, while the shivering rate was significantly higher in the other two groups. In addition, shivering in the placebo group was higher in comparison with the ketamine ($P = 0.0001$), but the nausea-vomiting incidence was not seen in recovery among the three groups [Table 5].

Table 1: Comparison of age and sex of patients

Groups	Dexmedetomidine	Ketamine	Placebo	P
Age mean (Year)	74.5±2.9	75.3±3.8	74.8±3.1	P=0.8
Sex				
Male	35.7%	34.9%	35.2%	P=0.6
Female	64.3%	65.1%	64.8%	

Table 2: Average scores of pain in patients

Groups	Dexmedetomidine	Ketamine	Placebo	P
VAS recovery	0	1.7±0.3	2.1±0.8	P=0.01
VAS 4 h after surgery	1.1±0.2	2.7±0.6	3.1±0.85	P=0.01
VAS 12 h after surgery	2.1±1.1	2.7±0.9	3.2±1.3	P=0.06
VAS 24 h after surgery	2.4±0.75	2.8±1.1	3.4±1.2	P=0.1

There were not any significant differences between the three studied groups in terms of mean blood pressure and heart rate. The average MAP and PR were the same in the three groups at the above-mentioned time. However, the heart rate of patients in the dexmedetomidine group was lower in PR recovery when comparing with other two groups, but the available differences were not significant ($P = 0.3$) [Table 6].

Discussion

In this study, we compared the effect of adding two dexmedetomidine and ketamine adjuvants in combination with bupivacaine to increase postoperative analgesia. According to the study achievements, in the dexmedetomidine group, the mean scores of pain were significantly lower in recovery and over the 4 h postoperative period, when comparing with the other two groups (ketamine and placebo), in other words, dexmedetomidine had a better postoperative analgesia as compare to other groups. Furthermore, findings demonstrated that drugs used during the operation and over the 4 h postoperative period in the dexmedetomidine group were lower than the other two groups, which again confirmed that dexmedetomidine is effective in the reduction of postoperative pain and their opiate medication. Additionally, investigation of other results demonstrated that there weren't any differences between hemodynamic parameters in the three groups and therefore, dexmedetomidine did not reveal a negative correlation with hemodynamics.

Previous studies have been closely aligned with our study, where Kararmaz *et al.*, in 2003, investigated the effects of ketamine IV and epidural anesthesia, they indicated that the use of ketamine IV was capable of reducing postoperative pain score.^[14] This result was consistent with our study because ketamine in our study also caused postoperative analgesia.

Another study by El-Rahmawy evaluated the effects of dexmedetomidine combined with bupivacaine on the quality of blind fascia iliaca compartment block (FICB) in children with femoral fractures. combined use of bupivacaine–dexmedetomidine exhibited end-tidal sevoflurane concentration

was decreased for fascia iliaca compartment block, leading to increased postoperative analgesia. Moreover, due to the significant reduction in end-tidal sevoflurane consumption during surgery, the hemodynamics of the children became more stable during surgery.^[15] The achievements of their study were in line with the results of ours, such a way that we demonstrated that dexmedetomidine increases the postoperative analgesia duration in patients who undergo femoral fracture operation. The use of opioid in the dexmedetomidine group was clearly reduced during surgery, which was consistent with aforementioned study.

Paying attention to the problems and illnesses associated with the elderly is one of the important priorities of the health system. In the elderly age group, the fracture of the femoral bone is one of the most common health problems. Administering regional anesthesia techniques, particularly epidural anesthesia, is of great help to physicians for anesthesia and postoperative pain control, where has great benefits for these elderly patients.^[16] The aim of the addition of adjuvant drugs to 0.5% bupivacaine is one of the goals of anesthesiologists in the management of patients with lower limb fracture, especially femoral fracture, in order to control postoperative pain and increase patient satisfaction.^[17]

Priye *et al.*, in 2015, have investigated the effect of dexmedetomidine infusion in in postcardiac surgery patients. Based on their reports, the VAS score in the placebo group was significantly lower in comparison with the placebo group. In addition, Incidence of delirium after the operation was significantly lower in the dexmedetomidine group as compared to placebo group.^[18] Moreover, their findings were also in line with the results of the present study, which emphasizes the effectiveness of dexmedetomidine on postoperative analgesia.

In their study, Arunkumar *et al.* conducted a comparative study on the effectiveness of clonidine and dexmedetomidine (two adjuvants to epidural ropivacaine) for epidural anesthesia. They found that the onset and duration of sensory blockade, and sedation were markedly favorable in the dexmedetomidine group, where the use of dexmedetomidine was associated with faster onset, prolonged duration of action with better sedation.^[19] This

Table 3: Average drug intake during the operation 24 h after surgery

Groups	Dexmedetomidine	Ketamine	Placebo	P
Narcotic average during surgery (μ)	5 \pm 1.1	30 \pm 4.1	35 \pm 3.9	$P=0.001$
Narcotic average during surgery 24 h after (mg)	37.5 \pm 4.6	91.5 \pm 7.7	92.5 \pm 9.8	$P=0.01$

Table 4: The mean duration of analgesia and score in recovery

Groups	Dexmedetomidine	Ketamine	Placebo	P
Period of analgesia in hours	10.7 \pm 2.4	2.1 \pm 2.4	1.7 \pm 1.1	$P=0.001$
Coded average of score in recovery	1	1	1	$P\geq 0.05$

Table 5: Incidence of shivering and nausea-vomiting

Groups	Dexmedetomidine	Ketamine	Placebo	P
Incidence of shivering	0	40%	60%	$P=0.0001$
Incidence of nausea-vomiting	0	0	0	$P\geq 0.05$

Table 6: The heart rate and average blood pressure of patients before and during the recovery period

Groups	Dexmedetomidine	Ketamine	Placebo	P
MAP pre-operation	98.7±5.6	97.1±7.7	94.4±6.9	P=0.7
PR pre-operation	73.6±8.1	74.9±6.2	75.4±4.9	P=0.8
MAP recovery	81.9±4.7	83.8±5.8	81.9±5.9	P=0.6
PR recovery	69.6±5.6	75.8±4.4	73.6±4.6	P=0.3

study was also consistent with our study, where the significant effect of dexmedetomidine as an adjuvant on increasing the duration of analgesia and the quality of the block is mentioned.

Kamali *et al.* (2013) conducted a study on patient's candidates for elective surgery of femur fracture to evaluate the effectiveness of adding ketamine and neostigmine to bupivacaine 0.25% on postoperative analgesia. They showed that the administration of Ketamine and Neostigmine with bupivacaine 0.25% could increase the duration of postoperative analgesia and also decrease the consumption of analgesic agent in epidural anesthesia, where were found to be effectively used by applying Ketamine as compared to neostigmine. In accordance with our study, aforementioned study demonstrated the effect of ketamine on reduction of opioid consumption and increment of postoperative analgesia duration. Overall, the findings indicate the effect of dimethomidine and ketamine in increasing the time duration of postoperative analgesia, while the effect in the dexmedetomidine group is far higher than that of ketamine.

The capability of assessing the success rate in the regional nerve blockade was one of the main limitations of the present study. Additionally, the lack of possibility of evaluating the degree of postoperative sedation is another limitation of this study that may be due to the adverse effects of ketamine and dexmedetomidine administration. Where possible, we attempted to update the available pathologic information, however further studies with full pathologic reviews would be desirable to confirm these findings.

Conclusion

Both ketamine and dexmedetomidine, as an adjuvant drug, increased the duration of postoperative analgesia and the quality of the block for epidural anesthesia. However, dexmedetomidine is clearly more effective than ketamine.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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