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ORIGINAL ARTICLE

Effect of Ketamine on the Quality of Anesthesia and Postoperative Analgesia in Epidural Anesthesia

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ABSTRACT

Purpose: To investigate the additional effects of ketamine to the epidural anesthesia over quality of intraoperative anesthesia and postoperative analgesia.

Methods: Sixty adult patients, aged 20–70 years with an American Society of Anesthesiologists physical status of I-III (ASA I-III) who were scheduled for total hip arthroplasty were enrolled. A 18-gauge epidural needle from the L4-5 space in addition to bupivacaine 75 mg; fentanyl 100 mcg was delivered in Group BF, ketamine 30 mg in Group BK, and fentanyl 100 μg plus ketamine 30 mg in Group BKF. Onset time of sensory block, start time of surgery, maximal sensory block level, time to two-segment regression, length of anesthesia, motor block level, quality of anesthesia, and patient satisfaction were determined. At the end of the operation, analgesia was achieved by patient-controlled analgesia method. Time to first analgesic requirement, morphine consumption at 24 hours, number of requests for additional analgesic, and the amount of delivered bolus solution, were noted.

Results: There was no statistically significant difference between the groups with regard to onset time of sensory block and length of surgery. Start time of surgery was significantly shorter in Group BKF; and time to two-segment regression, length of anesthesia, and time to first analgesic requirement were significantly longer in Group BF. Morphine consumption at 24 hours, number of requests for additional analgesic, and the amount of delivered analgesic bolus were minimal in Group BKF.

Conclusion: Epidural ketamine shortened the start time of surgery by reducing the onset time of block and elevating the maximal block level.

1. Introduction

Postoperative pain is an acute pain that starts with a surgical trauma and decreases gradually as the tissue healing takes place. Tissue damage and accompanying stress responses lead to physiologic and metabolic changes. Blockage or reduction of the stress response facilitates healing by reducing catabolism and accelerating the passage to the anabolic phase.

Recently, initialization of analgesic therapy prior to surgical intervention has increasingly been applied to postoperative pain management. The aim of those procedures, which are termed "preemptive analgesia", can be summarized as a reduction of postoperative analgesic requirement and prevention of perioperative spinal hyperexcitability.[1] Despite the widespread use of opioids in combination with local anesthetics in preemptive analgesia, it has some life-threatening complications such as respiratory depression.

N-methyl-D-aspartate (NMDA) receptors taking part in the central sensitivity mechanism have been shown to play a role in the postoperative pain development by various studies. Ketamine, a noncompetitive NMDA receptor antagonist, is employed at subanesthetic doses for intra- and postoperative pain management. An addition of ketamine to the combination of local anesthetic and opioid in epidural anesthesia may reduce those complications by lowering the dose of opioid. Although there are studies indicating that epidural ketamine increases the effect of epidural morphine,[2–4] in a study conducted on rats, it has been reported to have no influence over the effect of epidural fentanyl.[2]

Conflicts of interest: There is no conflicts of interest.

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The aim of the present study is to investigate the effects of ketamine addition to epidural anesthesia, performed with bupivacaine and fentanyl, on the quality of intraoperative anesthesia and postoperative analgesia in total hip arthroplasty.

2. Methods

Sixty adult patients, aged between 20 years and 70 years and having an American Society of Anesthesiologists (ASA) physical status of I-III, who were scheduled for total hip arthroplasty, were enrolled in the present study following the approval of the Ethics Committee of Ankara Numune Training and Research Hospital (Ankara, Turkey) and acquisition of patients' informed consents. Cases with a physical status of greater or equal to ASA physical status of IV, anesthesia risk, difficulty in placement of epidural catheter, hip prosthesis due to revision, difficulty in cooperation and orientation, contraindication for regional anesthesia, known history of allergy to local anesthetics, and difficulty in using patient-controlled analgesia device were excluded from the study.

In the preoperative assessment, patients were informed about the anesthesia methods to be used in the operations, verbal pain scale, and usage of patient-controlled analgesia (PCA) device. All patients received 10 mL/kg of 0.9% isotonic sodium chloride infusion for prehydration purposes.

According to a computer-generated table of random numbers, patients were allocated. After being taken to the operating room, patients' heart rate, noninvasive blood pressure, respiratory rate, oxygen saturation (with pulse oximetry), and EKG; electrocardiocraphi (ECG) (Draeger PM 8060 Vitara, Germany) were monitored, and the values were recorded prior to the block.

Epidural anesthesia was performed at the sitting position, by the loss of resistance technique, with a 16-gauge Tuohy needle (Epidural Minipack Portex, Smiths Medical, Kent, UK), under required asepsis conditions, using a local anesthesia of 2% prilocaine 2 mL. With the open tip of the needle toward the cranium, the epidural catheter was advanced by the catheter advancement technique. After verifying the catheter to be in the epidural space and observing no cerebrospinal fluid (CSF) or blood, it was fixated 3–4 cm within the epidural space. Patients assumed the supine position.

Apart from the delivery of a standard 0.5% bupivacaine (Marcain 0.5%; Astra Zeneca, London, UK) dose of 75 mg/15 mL to all the groups, the bupivacaine and fentanyl group (Group BF) received fentanyl 100 μg/3 mL (fentanyl citrate 500 μg/10 mL; Abbott, Abbot Park, Illinois, USA), the bupivacaine and ketamine group (Group BK) received ketamine 30 mg/3 mL (Ketalar 500 mg/10 mL; Pfizer, New York, NY, USA), and the bupivacaine, ketamine, and fentanyl group (Group BKF) received a combination of fentanyl 100 μg/2 mL and ketamine 30 mg/1 mL, all of which had a volume of 18 mL; the users were blinded to the study solutions.

Sensory and motor block levels were evaluated and recorded at 1 to 90 minutes, and every 30 minutes postoperatively until the sensory block decreased to L2 dermatome level or reached a Bromage score of 0.

The sensory block was determined using the pin-prick test with a 22-gauge needle tip, whereas the Bromage score was used for the assessment of the motor block (0: no motor block; 1: able to flex the knee and move the foot, but unable to raise the leg; 2: only able to move the leg; and 3: unable to move the foot and knee).

The onset time of the sensory block was determined. The operation was allowed when the sensory block level reached the T10 dermatome level. The onset of sensory block at the T10 dermatome level was noted as the start time of surgery, whereas the time to complete the disappearance of the sensory block was noted as the length of anesthesia. The maximal sensory block level, motor block levels, and time to two-segment regression were all recorded. The interval between the beginning and end of the operation was recognized as the length of the operation.

Hemodynamic parameters were noted at 5-minute intervals. In all patients, a 25% reduction in the baseline systolic blood pressure was recognized as hypotension and treated slowly with iv ephedrine 10 mg. Atropine 0.5 mg was delivered via iv route in patients with a heart rate below 50 beats/minute. The total amount of ephedrine and atropine delivered was recorded.

Following the operation, each patient was connected to the PCA device (Abbott). The analgesic solution was prepared with 0.2 mg/mL morphine in 150 cm^3 0.9% NaCl. As the loading dose, morphine 2 mg was delivered into the epidural space. The PCA device was set to have 0.1 mg/hour infusion speed and 0.2 mg bolus dose, whereas the lockout time was fixed to 15 minutes. The time to first analgesic requirement was recognized as the time to first bolus dose requirement.

The Verbal Pain Scale scores, pain levels, number of requests, number of requests met by the PCA device, and amount of solution consumed by the PCA device at 0 hour, 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, and 24 hours were evaluated (0: no pain; 1: mild pain; 2: moderate pain; 3: severe pain; and 4: very severe pain).

In terms of side effects, all the patients were evaluated for nausea, vomiting, pruritus, hypotension, urinary retention, flushing, vasovagal reflex, respiratory depression, and hemodynamic parameters at hours (0, 1, 2, 4, 8, 12, and 24).

Moreover, at the end of the operation, patients were verbally inquired about the quality of anesthesia and patient satisfaction (they were asked to rate those items as very good, good, or poor), while their answers were recorded. Quality of anesthesia was assessed as follows: very good, patient satisfied and comfortable during the procedure; good, complete analgesia achieved, but complaints about undefined discomfort and requirement of sedation; inadequate: absence of complete anesthesia, complaints about strain pain, painful hip movements, and requirement of anesthesia (50 mg propofol iv); and unsuccessful: inadequate analgesia and conversion to general anesthesia.

2.1. Statistical analysis

Data were analyzed with Statistical Package for Social Science version 11.5 (SPSS Inc., Chicago, Illinois, USA). Calculations from the pilot studies showed that 15 patients per group would allow the detection of a difference of 20% in postoperative morphine consumption, with an overall α error at the 0.05 level and 80% power. Continuous variables were expressed as mean and standard deviation or median (minimum–maximum) values, whereas categorical variables were demonstrated as percentages. Shapiro–Wilks test revealed that continuous variables were not verifying the parametric test estimations. Comparisons across groups were carried out with Kruskal–Wallis variance analysis. Intragroup comparisons were performed with Friedman test, using Bonferroni correction. In order to determine the origin of the difference occurring over time, Friedman multiple comparison tests were conducted. Categorical comparisons were accomplished by Chi-square test. A p value of <0.05 was recognized as statistically significant.

3. Results

No statistical difference was observed between the groups with regard to age, weight, height, sex distribution, or ASA physical status scores (Table 1). Although no statistically significant difference was detected between the groups relative to the onset time of the sensory block and length of operation, the start time of surgery

Table 1 Demographic characteristics.

	BF	BK	BKF
Age (yr)	52. 8 ± 8. 03	50. 50 ± 7. 49	53. 50 ± 9. 8
Weight (kg)	70. 3 ± 12. 57	67. 85 ± 10. 60	73. 84 ± 9. 74
Height (cm)	158, 15 ± 5. 68	158. 05 ± 9.01	159. 7 ± 7. 76
Sex, F/M	15/5	14/6	13/7
ASA, I/II/III	5/7/8	4/10/6	5/7/8

M = male; F = female; ASA I/II/III = American Society of Anesthesiology physical status; B+F = Group Bupivacaine and Fentanyl; B+K = Group Bupivacaine and Ketamine; B+F+K = Group Bupivacaine and Fentanyl and Ketamine (mean ± standard deviation).

was significantly shorter in Group BKF, and the time to two-segment regression, length of anesthesia, and time to first analgesic requirement were significantly longer in Group BF (Figure 1).

With regard to motor and sensory blocks, all three groups were evaluated to predominantly have a Bromage score of 1 for motor block, and no significant difference was detected between the groups. Maximal sensory block levels were highest in Group BKF and the difference was found to be statistically significant ($p < 0.001$).

In the assessment of intraoperative hemodynamic parameters, no statistically significant difference was observed between the groups with regard to heart rates at all times. Intragroup evaluations revealed clinically insignificant, but statistically significant changes at minutes (45, 60, and 75) in Group BK, and at minutes (20, 30, 45, 60, and 75) in Group BKF (Figure 2).

No statistically significant difference was found between the groups in terms of systolic blood pressure at all times. Intragroup analyses demonstrated decreases between the 5th minute and 90th minute after the block in Group BF; at minutes (5, 30, 45, 60, and 75) in Group BK; and at 60 minutes in Group BKF (Figure 3).

In terms of saturation levels and respiratory rates, no statistically significant change was observed in the intra- and intergroup analyses.

In view of the postoperative hemodynamic parameters, no statistically significant change was found in the intra- and intergroup analyses with regard to heart rates (Table 2).

No statistically significant change was observed in the inter- and intragroup analyses relative to systolic blood pressures (Table 3).

In the analysis of postoperative verbal pain scores, four (20%) patients in Group BF, three (15%) in Group BK, and two (10%) in Group BKF complained of moderate pain at the time to first analgesic requirement. No moderate or severe pain was observed in the assessments performed from 1 hour onward. No difference between the groups with regard to verbal pain scores was reported.

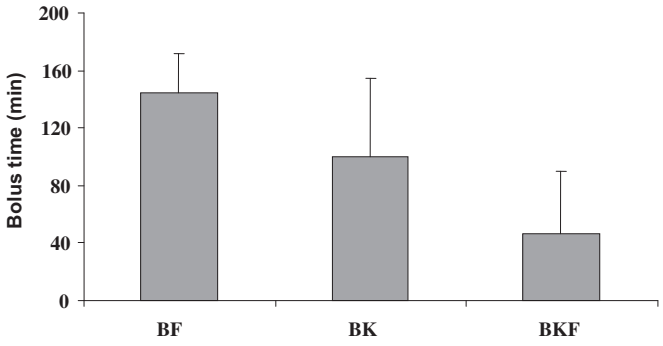

Figure 1 Times to first analgesic requirement. BF = Group Bupivacaine and Fentanyl; BK = Group Bupivacaine and Ketamine; BFK = Group Bupivacaine and Fentanyl and Ketamine.

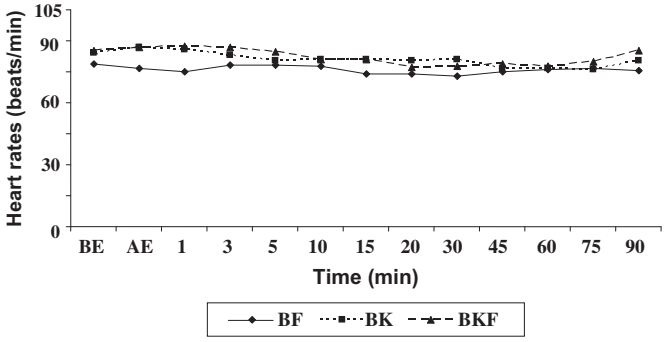

Figure 2 Changes in the intraoperative heart rates over time. BF = Group Bupivacaine and Fentanyl; BK = Group Bupivacaine and Ketamine; BFK = Group Bupivacaine and Fentanyl and Ketamine; BE = before epidural; AE = after epidural.

Morphine consumption at 24 hours was lowest in Group BKF and highest in Group BF. This value was found to be statistically significant. Similarly, the number of requests for additional analgesic and the amount of bolus solution delivered by the device were lowest in Group BKF and highest in Group BF. Those results were found to be statistically significant (Figures 4 and 5).

In view of the side effects during intra- and postoperative periods, one patient in Group BK demonstrated hallucination; four patients in Group BF, two individuals in Group BK, and four individuals in Group BKF showed hypotension; two patients from each group exhibited bradycardia, whereas one patient from each group showed nausea; and one patient from Group BF and Group BK each displayed vomiting. In the postoperative period, although none of the patients exhibited hallucinations, 15 individuals in Group BF, 10 individuals in Group BKF, and eight individuals in Group BK demonstrated nausea; 11 patients in Group BF, nine patients in Group BK, and seven patients in Group BKF showed vomiting; six individuals in Group BF and three individuals in Group BK displayed pruritus; and two patients in Group BK manifested urinary retention. In terms of side effects, only pruritus was more frequently observed in Group BF, and this difference was found to be statistically significant (Table 4).

Quality of anesthesia and patient satisfaction were very good in 80% of the patients in Group BF and good in the remaining 20%, whereas those were very good in 100% of patients in Groups BKF and BK. None of the groups demonstrated inadequate anesthesia that would require additional sedation.

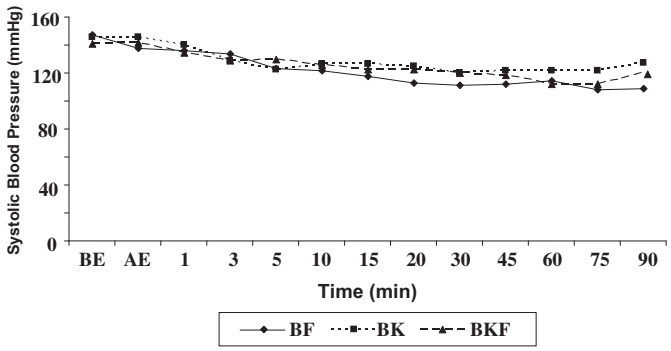

Figure 3 Changes in the intraoperative systolic blood pressures over time. BF = Group Bupivacaine and Fentanyl; BK = Group Bupivacaine and Ketamine; BFK = Group Bupivacaine and Fentanyl and Ketamine; BE = before epidural; AE = after epidural.

Table 2 Postoperative heart rates.

Time (h)	Heart rate (beats/min)		
	BF	BK	BKF
0	81.5 ± 13.6	83.4 ± 12.6	90.9 ± 16.9
1	81.9 ± 13.6	84.6 ± 15	89.1 ± 16.7
2	82.1 ± 15.2	84.1 ± 13.6	90.0 ± 13.8
4	82.7 ± 11.3	84.8 ± 8.5	82.6 ± 9.3
8	81.7 ± 11	81.2 ± 6.1	86.2 ± 10.8
12	82.8 ± 9.9	82.1 ± 5.9	87.3 ± 9.5
24	83.4 ± 6.8	82.3± 6.1	88.0 ± 11.5

BF = Group Bupivacaine and Fentanyl; BK = Group Bupivacaine and Ketamine; BFK = Group Bupivacaine and Fentanyl and Ketamine.

Table 3 Postoperative systolic blood pressures.

Time (h)	BP (mm Hg)		
	BF	BK	BKF
0	119.5 ± 21.2	122.8 ± 17.0	122.8 ± 14.28
1	114.2 ± 20.7	115.4 ± 17.8	115.2 ± 21.75
2	118.0 ± 18.3	113.7 ± 20.0	111.6 ± 17.56
4	115.6 ± 14.7	120.5 ± 17.2	116.0 ± 15.69
8	116.1 ± 17.1	122.1 ± 11.4	116.0 ± 11.77
12	117.2 ± 9.0	119.5 ± 13.0	118.3 ± 14.89
24	120.0 ± 12.3	120.4 ± 13.1	109.5 ± 16.38

BF = Group Bupivacaine and Fentanyl; BK = Group Bupivacaine and Ketamine; BFK = Group Bupivacaine and Fentanyl and Ketamine.

4. Discussion

Regional anesthesia has been shown to improve the course of certain surgical conditions. It reduces deep vein thrombosis, pulmonary embolism, intraoperative blood loss, and need for transfusion. Pulmonary embolism, developing after total hip arthroplasties carried out under epidural anesthesia, is observed less frequently. A retrospective study has shown that mortality after total hip arthroplasty occurs six times more frequently with general anesthesia compared with the epidural anesthesia. Similarly, epidural anesthesia reduces the incidence of deep vein thrombosis and intraoperative blood loss in total hip arthroplasty procedures.[5] In order to increase the quality of intraoperative epidural anesthesia and establish postoperative analgesia, adding opioids to the local anesthetics is a widespread practice. The opioid that is most frequently used for this purpose is fentanyl, due to its rapid onset of action, less side effects, and the ability to prolong the length of block.

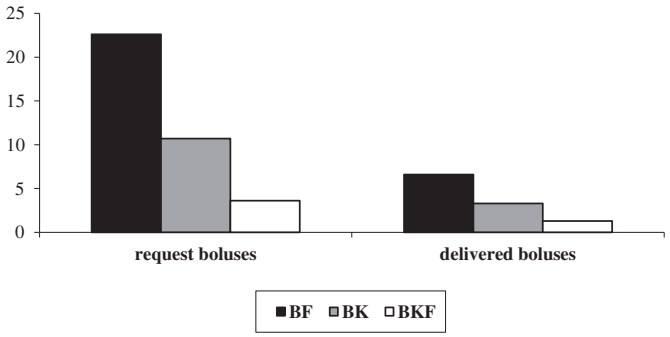

Figure 4 Number of requests and the amount of delivered boluses at 24 hours. BF = Group Bupivacaine and Fentanyl; BK = Group Bupivacaine and Ketamine; BFK = Group Bupivacaine and Fentanyl and Ketamine.

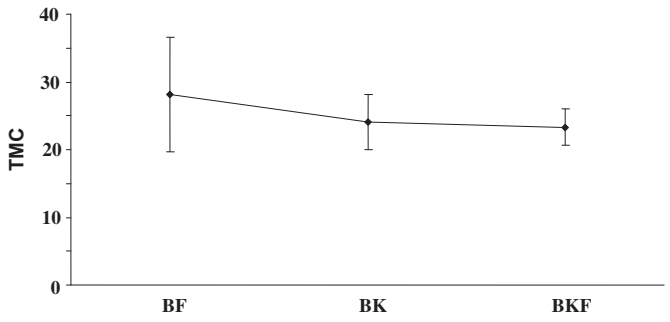

Figure 5 Total morphine consumption (TMC) at 24 hours. BF = Group Bupivacaine and Fentanyl; BK = Group Bupivacaine and Ketamine; BFK = Group Bupivacaine and Fentanyl and Ketamine.

Table 4 Intraoperative and postoperative side effects.

Side effects		BF (%)	BK (%)	BKF (%)	*p*-value
Intraoperative	Nausea	1 (5)	1 (5)	1 (5)	1
	Vomiting	1 (5)	1 (5)	0 (0)	0.596
	Bradycardia	2 (10)	2 (10)	2 (10)	1
	Hypotension	4 (20)	2 (10)	4 (20)	0.619
	Hallucination	0 (0)	1 (5)	0 (0)	0.260
Postoperative	Nausea	15 (75)	8 (40)	10 (50)	0.072
	Vomiting	11 (55)	9 (45)	7 (35)	0.446
	Pruritus*	6 (30)	3 (15)	0 (0)	0.029
	Urinary retention	0 (0)	2 (10)	0 (0)	0.126

BF = Group Bupivacaine and Fentanyl; BK = Group Bupivacaine and Ketamine; BFK = Group Bupivacaine and Fentanyl and Ketamine. *$p < 0.05$ was recognized as statistically significant.

Parenteral opioid therapy is the gold standard in nociceptive pain treatment; however, better and long-term analgesia is achieved by epidural opioids.[6] In the postoperative period, compared with the systemic analgesics, epidural analgesia reduces pulmonary and cardiovascular morbidity, accelerates recovery, and facilitates a faster exit from intensive care.[7,8] Although the epidural morphine dose required for postoperative analgesia is approximately one-tenth of the morphine dose used via intramuscular route, several side effects such as respiratory depression, nausea, and vomiting have been reported.[9] In order to decrease the incidence of side effects and increase the analgesic efficacy, the term "balanced analgesia" has been proposed.[10] Some of the agents used for increasing the analgesia achieved by opioids are NMDA receptor antagonists.[2]

Analgesic effects of ketamine, a noncompetitive NMDA receptor antagonist, were first described 30 years ago.[11] In many clinical studies performed during the past 15 years, the role of ketamine in the prevention and management of postoperative pain has been investigated. The use of low-dose ketamine (0.1-0.5 mg/kg), in combination with local anesthetics, opioids, or other analgesics, may play a significant role in postoperative pain management.[12]

Epidural ketamine has been found to selectively potentialize the effect of epidural morphine, whereas it has been shown to exhibit a tendency toward antagonizing the nociceptive effects of fentanyl.[2] In the current study, an addition of ketamine to the bupivacaine and fentanyl combination decreased the start time of surgery, time to two-segment regression, length of anesthesia, and time to first analgesic requirement, but increased the maximal sensory block level.

According to Kawana et al,[13] when delivered alone, epidural ketamine shows a less analgesic effect compared with the opioids, whereas it shortens the onset of epidural anesthesia when administered in combination with bupivacaine.[14] However, Weir and Fee[15] added varying doses of ketamine to the bupivacaine anesthesia applied to patients undergoing knee arthroplasty and found no difference with regard to sensory block at 20 minutes. In the current study, the onset time of sensory block was found to be 2.9 minutes in Group BF, whereas 3.0 minutes and 2.3 minutes in Groups BK and

BKF, respectively; however, the difference was not statistically significant. In view of those results, we cannot claim that ketamine shortened the bupivacaine onset of action, because there was no bupivacaine-alone group. However, onset of epidural anesthesia occurs within 5–15 minutes for anesthetics with a rapid onset of action. Bupivacaine has a slower onset of action compared with those anesthetics.[16] Moreover, the addition of ketamine to local anesthetics is known to reduce the onset of action.[17] Adding ketamine to bupivacaine renders the onset of action similar to that of the bupivacaine and fentanyl combination. Furthermore, using ketamine with a bupivacaine and fentanyl combination shortens this time even further. Our results were consistent with those of Yanli and Eren.[14] Weir and Fee[15] mentioned the onset of action only at 20 minutes and did not report the earlier times. Collins[18] reports that ketamine can inhibit action potentials by affecting sodium and potassium channels, and therefore can demonstrate the influence of local anesthetics. Those local anesthetic properties may have a role in accelerating the onset time of sensory block in epidural anesthesia.

Yanli and Eren[14] reported that the ketamine plus bupivacaine combination elevated the sensory block level. Weir and Fee[15] found no difference at 20 minutes with regard to the block level. Nonetheless, although they determined no significant difference, the level of block increased as the dose of epidural ketamine was raised. In the present study, T2–4 block level was observed in one patient of Group BF, seven patients of Group BK, and 18 patients of Group BKF. Although the median value was T6 in both Group BF and Group BK, it was T2 in Group BKF. This difference was statistically significant. The epidural anesthesia level is influenced by physical factors such as injection site, volume of the delivered epidural solution, concentration and total volume of the delivered drug, speed of injection, patient's position, and age, height, and weight of the patient.[19] Epidural drug diffuses into the CSF and spinal cord, depending on the dural thickness as well as on the drug's density, lipid solubility, and molecular structure. Opioids that are less lipid soluble demonstrate lower uptake by tissue and receptors, which leads to their elevated levels in the CSF.[20] Competition between fentanyl and ketamine is based on receptors, and therefore it may raise the free amount of drug, thus being responsible for the elevated anesthesia level. In light of those data, the results of our study are consistent with those of the study of Yanli and Eren.[14] The addition of ketamine to bupivacaine and bupivacaine and fentanyl combination raises the maximal block level.

The start time of surgery was 7.5 minutes in Group BF, but 7.5 minutes and 6.1 minutes in Groups BK and BKF, respectively; the difference was statistically significant. This difference may be associated with the rapid onset of the sensory block and a high level of maximal block in Group BKF. In the study of Weir and Fee,[15] the block level was L1 at 5 minutes and T8 at 10 minutes in the group that received an addition of ketamine 0.5 mg/kg to bupivacaine. The block level reached T10 at 5 minutes by the addition of ketamine 0.67 mg/kg. The start time of surgery in our study was consistent with those results.

The time to two-segment regression was 197.7 minutes in Group BF, but 109.5 minutes and 121 minutes in Groups BK and BKF, respectively. The length of anesthesia was 252.5 minutes in Group BF, but 191 minutes and 213.5 minutes in Groups BK and BKF, respectively. The time to first analgesic requirement was 144.3 minutes in Group BF, 99.8 minutes in Group BK, and 46.8 minutes in Group BKF. Differences between Groups BF and BKF were statistically significant. Bupivacaine and fentanyl combination is known to prolong the duration of anesthesia. In the present study, using ketamine in combination with bupivacaine did not change the duration of action of bupivacaine. Similarly, Himmelseher et al[20] found no remarkable changes in the length of anesthesia upon addition of S(+)-ketamine to ropivacaine in their study. Epidural bupivacaine is known to have a 2–4-hour duration of action.[19] Results concerning the two-segment regression and length of anesthesia in Group BF correlated with the standard data.

Highly lipophilic anesthetic agents are considered to use passive diffusion for passage into the central nervous system. However, this opinion has been changed following the finding that lipophilic drugs, such as P-Glycoprotein, are carried by transport proteins.[21] Although no transport protein has been identified for fentanyl yet, Henthorn et al[22] have shown that it competes to pass the blood–brain barrier with both active and passive transport. Although the active transport of ketamine in the blood–brain barrier has not yet been demonstrated, the competition between ketamine and fentanyl for binding with the same transport protein will be one of the mechanisms of high-dose ketamine, which aims to reduce the antinociceptive properties of fentanyl.[2]

The interaction between fentanyl and ketamine alters the pH around blood–brain barrier, which may lead to differences in the passive diffusion. Theoretically, because of the steric competition between ketamine and fentanyl, one of them inhibits the diffusion of the other.[2] Moreover, an interaction at receptor level may take place as well. Although fentanyl and morphine have been shown to bind with the α, β, and μ receptors at varying degrees, Matthes et al[23] found that morphine exhibited its antinociceptive properties through μ receptors. Ketamine binds with μ receptors as well; however, the antinociception generated by ketamine apparently takes place via a nonopioid mechanism.[24] The combination of two lipophilic and rapid agents such as ketamine and fentanyl may cause a competition over μ receptors. Thus, fentanyl binds with fewer μ receptors. Therefore, antinociception achieved by fentanyl is partially antagonized with ketamine.[2]

Recently, differences have been shown in the clinical efficacies of various μ opioid receptor antagonists, which can be explained by the presence of more than one μ receptor subtypes.[25] Therefore, fentanyl and ketamine may bind to different receptor subtypes.[2] The differences in our study may be stemming from that mechanism.

In the current study, no difference was observed between the groups regarding the motor block. The motor block level was found to have a Bromage score of 1 in each group. Motor weakness may be due to local anesthetic or neurotoxic effects of ketamine. Lately, racemic ketamine has been reported to have neurotoxic properties. This toxicity is believed to be originating from the use of chlorobutanol as a preservative.[26] Different results have been obtained from neurotoxicity studies using benzethonium chloride as a preservative. Although its intrathecal usage is reported to cause no neurotoxicity among monkeys,[27–29] high doses of intrathecal delivery may lead to spinal myelopathy.[29] In the present study, the absence of changes associated with the motor block suggests that our doses were not associated with any clinical toxicity.

Little information is available on pharmacokinetics of epidural ketamine. A study on dogs[30] shows that racemic ketamine rapidly passes into CSF via the epidural space and demonstrates a prolonged plasma half-life compared with iv delivery. In humans, single-dose epidural ketamine 5 mg rapidly joins the systemic circulation and demonstrates 80% bioavailability.[31] In the present study, no significant difference was observed with regard to hemodynamic parameters. Moreover, blood pressure drops associated with epidural anesthesia were less in the ketamine group.

Morphine is a commonly used narcotic in postoperative pain management. Epidural morphine induces analgesia without causing sensory, sympathetic, and motor block.[3] Epidural use of morphine, even at lower doses, provides better and longer analgesia, with fewer side effects. Nonetheless, respiratory depression

may arise as a serious complication, particularly among elderly patients.[3] A combination of ketamine and epidural morphine may reduce the side effects associated with narcotics.

Studies that investigate the influence of ketamine on postoperative analgesia focus mainly on two issues: the time of ketamine delivery (pre- and post-operative) and ketamine dose. In the study of Wu et al,[32] multimodal preincisional analgesia performed with morphine, bupivacaine, and ketamine was found to be better than the postincisional one, whereas in the study of Choe et al,[33] preemptive analgesia conducted with morphine and ketamine was found to provide better postoperative pain management compared with the postoperative management.

Lahtinen et al[34] conducted a study using S(+)-ketamine iv, and found a prolonged time to first analgesic requirement and lower oxycodone consumption in the ketamine group. In the study of Sen et al,[12] a combination of low-dose ketamine iv (0.15 mg/kg) and intrathecal bupivacaine was demonstrated to induce longer postoperative analgesia and less postoperative analgesic consumption, compared with the bupivacaine-alone delivery. Aveline et al[35] found that a combination of preoperative low-dose ketamine and morphine led to a decrease in the postoperative morphine consumption and VAS scores, with fewer opioid-related side effects. Kwok et al[36] showed that preincisional ketamine iv prolonged the time to first analgesic requirement and lowered morphine consumption. Fu et al[37] found that preoperative ketamine, delivered as bolus via the iv route, reduced opioid consumption. Those studies demonstrate that ketamine harbors dominant supraspinal effects and activates monoaminergic descending inhibitory system.

Pharmacokinetic studies show that epidural ketamine use leads to higher CSF levels and prolonged half-life compared with the iv delivery.[38] Therefore, as the duration of action is prolonged, the effect of ketamine over postoperative analgesia increases. Guedes et al[39] found that preoperative epidural ketamine provided a rapid and efficient analgesic control in the postoperative period, and that normal function was restored rapidly in the normal leg.

Following unilateral knee arthroplasty, Himmelseher et al[20] achieved analgesia by PCA involving ropivacaine delivery via the epidural route and observed reduced ropivacaine consumption at 48 hours in the ketamine group. In the study of Abdel-Ghaffar et al,[40] preoperative and postincisional epidural ketamine 30 mg was found to prolong the time to first analgesic requirement and reduce the total analgesic consumption. Naguib et al[4] showed that epidural ketamine 30 mg established adequate postoperative analgesia in small abdominal surgeries, whereas Schmid et al[41] demonstrated that, below the dose of 1 mg/kg, epidural ketamine could play a significant role in postoperative pain management, only if used in combination with local anesthetics, opioid, or other analgesic agents. In the study of Wong et al,[3] epidural ketamine was shown to establish no important analgesic effect in major knee replacement operations, whereas its combination with morphine was demonstrated to generate adequate postoperative analgesia by potentializing the analgesic effects of morphine. Ozyalcin et al[42] showed that preoperative epidural ketamine reduced the need for intra- and postoperative analgesia, along with decreasing the postoperative hyperalgesia and allodynia associated with touch.

Contrary to those studies, Subramaniam et al[38] conducted a study where they delivered preoperative epidural morphine and ketamine combination and found no changes in the intraoperative morphine need, time to first analgesic requirement, and additional analgesic consumption. In the study of Kucuk et al,[43] epidural ketamine was found to have no influence on the postoperative pain management level, as well as no lowering effect on opioid consumption. Nonetheless, Subramaniam et al[44] conducted another study and found that postoperative epidural morphine and ketamine combination reduced the time to first analgesic requirement and additional morphine requirement. Taura et al[45] found that postoperative epidural morphine and ketamine combination prolonged the time to first analgesic requirement, while reducing the VAS scores and additional analgesic need.

In order to achieve better analgesia, we preferred to use preemptive ketamine 30 mg. Morphine consumption at 24 hours was 28.2 mL in Group BF, and was 24.1 mL and 23.3 mL in Groups BK and BKF, respectively. The number of requests for additional analgesic was 22.6 in Group BF, and was 10.7 and 3.6 in Groups BK and BKF, respectively. The amount of delivered boluses was 6.6 in Group BF, 3.3 in Group BK, and 1.3 in Group BKF. Those results were statistically significant for Group BKF and consistent with most of the abovementioned studies.

Nociceptive transmission and synaptic plasticity show a critical relationship with NMDA receptor activation.[21] NMDA receptors play a significant role in wind-up phenomenon and central sensitization caused by peripheral nociceptive stimulators.[38] Activated NMDA receptor has an influence over tolerance and unresponsiveness toward opioids.[38] NMDA receptor antagonists have been shown to inhibit the spinal advancement of nociceptive stimulation.[38] Ketamine not only eliminates the peripheral afferent painful stimulus, but also strengthens the opioid analgesia, by preventing central sensitization of nociceptors[42] and inhibiting the tolerance developed against opioids.[42] Ketamine shows its effects by binding to the specific phencyclidine region on the NMDA receptor channels, which are opened after the surgical stimuli.[46] Therefore, preoperative use of ketamine is believed to be more efficient than postoperative application.[46]

Gonzalez et al[47] showed that noncompetitive NMDA receptor antagonists reduced the physical dependence and the degree of tolerance. Laulin et al[48] demonstrated that the use of ketamine, prior to and after morphine delivery, prevented the development of long-term hyperalgesia. In the study of Hoffman et al,[2] ketamine was found to reinforce the antinociception induced by morphine, whereas it was not determined to reinforce the fentanyl-induced antinociception and was observed to even antagonize it.

In the current study, using morphine in the immediate postoperative period and employment of VAS for pain assessment prevented us from obtaining more objective postoperative pain scores. Lack of determination of sample sizes by preliminary studies was another shortcoming of the study. It is evident from our study that the use of preservative-free ketamine or S(+)-ketamine was safe for our patients. Nevertheless, none of our patients exhibited motor weakness.

Although there was no statistically significant difference in the postoperative period with regard to nausea, vomiting, and urinary retention, pruritus was seen in 30% of patients in Group BF. Preoperative epidural ketamine delivery reduced the side-effect incidence by decreasing the amount of morphine required to establish postoperative analgesia.

Following ketamine administration, psychomimetic side effects may also be observed. Those side effects vary depending on the ketamin's delivery mode and dose, as well as concomitant drug usage. In the current study, one patient from Group BK demonstrated hallucinations in the intraoperative period. Lahtinen et al[34] used ketamine iv in their studies and encountered hallucinations in 8% of patients. In epidural deliveries, except sedation, no side effect associated with the central nervous system was found. In our study, where we used single-dose ketamine, no sedation was determined among patients both in the intraoperative and in the postoperative periods. The reason behind this may be the usage of low-dose ketamine.

Balanced analgesia in postoperative pain management can be achieved by delivering epidural drugs with different effects. Ketamine, an NMDA receptor antagonist, is one of the drugs used for

this purpose. In our study, epidural ketamine shortened the start time of surgery by reducing the onset time of block and elevating the maximal block level. However, it antagonized the positive effects of fentanyl through decreasing the time to two-segment regression, length of anesthesia, and time to first analgesic requirement. Moreover, it reduced the postoperative morphine consumption and lowered the side-effect incidence by preventing opioid tolerance against fentanyl or acting as a preemptive analgesic. We believe that epidural racemic ketamine can be used routinely as a preemptive analgesic following a careful assessment of the balance between risks and benefits.

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