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Original Article

Effect of ketamine as an adjuvant in ultrasound-guided supraclavicular brachial plexus block: A double-blind randomized clinical trial study

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Abstract

Background: Supraclavicular brachial plexus block is one of the most effective anesthetic procedures in operations for the upper extremity. Ketamine has been reported to enhance the analgesic effects of local anesthetics. We have conducted this study to assess whether coadministration of ketamine can prolong the local analgesic effect of lidocaine in the supraclavicular brachial plexus block for patients undergoing elective upper extremity surgery.

Materials and Methods: Sixty adult patients undergoing elective surgery of the elbow, forearm, wrist or hand were randomly allocated in two groups of 30 patients each. Group 1 (ketamine group) received 5 mg/kg lidocaine 1.5% plus 2 mg/kg ketamine, Group 2 (control group) received 5 mg/kg lidocaine 1.5% and saline. The outcome measures included severity of pain by using visual analog scale (VAS, 0 = no pain 10 cm = the most severe pain), time of first request for analgesia, and total dose of postoperative opioid administration. The data was analyzed using the χ^2 test, student's t-test, Kaplan-Meier survival analysis, and Multivariate analysis tests.

Results: Patients in the control group had a higher VAS than patients who received ketamine, at all time points during the first 24 hours after surgery (all $P < 0.05$). The time of first request for analgesia in the ketamine group was significantly more than in the control group (8.93 ± 1.0 vs. 7.30 ± 1.9, respectively, $P < 0.001$).

Conclusion: The addition of ketamine to lidocaine in the ultrasound-guided brachial plexus block could decrease the postoperative pain and need for analgesic. Therefore, it could be considered as an option in the brachial plexus block to enhance the analgesic action of lidocaine.

Key Words: Anesthesia, ketamine, supraclavicular brachial plexus block

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INTRODUCTION

The supraclavicular brachial plexus block is a known anesthetic approach for upper extremity surgery.[1,2] The use of ultrasonic images has minimized the risk of complications.[3] Efforts have been made to enhance the outcomes of the block by adding various adjuncts to the anesthetic agent. Drugs such as opioids,[4] naloxone,[5]

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clonidine,[6] midazolam,[7] dexmedetomidine,[6] epinephrine,[8] and recently dexamethasone,[9] have been used along with local anesthetics for this purpose with varying degrees of success.

Ketamine is a noncompetitive antagonist of the N-methyl-D aspartate receptor (NMDAR). It is used for premedication, sedation, induction, and maintenance of general anesthesia.[10] Central, regional, and local anesthetic and analgesic properties have been reported for ketamine. Intravenous (IV) administration of low-dose ketamine decreases postoperative opioid use and improves analgesia.[11] The addition of ketamine to epidural lidocaine or bupivacaine increases the duration of regional anesthesia and postoperative analgesia.[12] It has been seen that peri-incisional use of 0.3-0.5% ketamine combined with local anesthetic in surgical wounds enhances analgesia by a peripheral mechanism.[13]

Several studies have been performed to evaluate the effect of added ketamine to local anesthetics for nerve block and regional anesthesia. Ketamine did not enhance the onset time and duration of sensory and motor blockade when added to ropivacaine for the interscalene brachial plexus block.[14] Addition of ketamine to ropivacaine infusion via the femoral nerve catheter after repairing an anterior cruciate ligament (ACL) injury/tear could not improve postoperative pain control.[15]

We conducted this study to evaluate the effect of ketamine added to lidocaine at the onset on the duration of sensory and motor block and postoperative pain in supraclavicular brachial plexus block for patients undergoing elective upper extremity surgery.

MATERIALS AND METHODS

This randomized, double-blinded, clinical trial was conducted between November 2012 and November 2013, in the two teaching hospitals (Ayatollah Kashani and Al-Zahra Hospital) of the Isfahan University of Medical Sciences. The study protocol was approved by the Ethical Committee of the University, and written informed consent was obtained from all the patients.

On the basis of the previous study,[13] a sample size of 30 per group was required in order to have a 30% difference in postoperative VAS between the case and control groups, with $\alpha = 0.05$ and $\beta = 0.2$. Sixty patients undergoing surgery for the elbow, forearm, wrist or hand were randomly allocated into two groups of 30 patients each. Group 1(ketamine group) received 5 mg/kg lidocaine 1.5% and 2 mg/kg ketamine in a total volume of 25 cc, while Group 2 (control group) received 5 mg/kg lidocaine 1.5% and saline in a total volume of 25 cc. The solution was prepared in the same syringe for each patient and all syringes were the same in shape and size. The study drugs were administered before beginning of surgery, at the time of the supraclavicular block.

Non-pregnant or lactating patients of age between 15 and 60 years, American Society of Anesthesiologists (ASA) class I-II, and body mass index (BMI) between 20 and 35 kg/m^2 were included. Other inclusion criteria were, no history of pre-existing neuropathy, coagulopathy, hepatic or renal impairment, severe pulmonary disease, allergy to drugs used in this study, infection at the injection site, prior surgery in the supraclavicular, infraclavicular or axillary regions, alcohol or drug abuse.

Patients with the duration of operation >120 minutes or <30 minutes, patients in whom the block success was not obtained 30 minutes after injection, those who showed an allergic reaction to the drugs, and those who did not cooperate or were not willing to participate in the study were excluded.

After arrival to the anesthetic room, the peripheral intravenous (IV) line was placed in the non-operative upper limb and an infusion started with normal saline. Supplemental oxygen (4 L/minute, was delivered by nasal cannula) and routine anesthesia monitoring, including noninvasive arterial blood pressure, heart rate, and pulse oximetry were applied. Midazolam of 0.04 mg/kg was administered intravenously to all patients as premedication, five minutes before giving the block.

The anesthetic solution was prepared by a nurse, not otherwise involved in the study. The resident who performed the block was blinded to the treatment group. All observations were carried out by a single investigator, who was also blinded to the treatment group.

The skin of the supraclavicular fossa was disinfected with a povidone-iodine solution of 10%. For the ultrasound-guided supraclavicular brachial plexus nerve block we used a SonoSite S Nerve (USA, Bothell, WA) ultrasound machine, with a linear high frequency (8-13 MHz) probe (covered with a sterile dressing).

The probe was positioned in a coronal oblique plane in the supraclavicular fossa, to perform an exploratory scan. The brachial plexus was visualized as a group of round or oval hypoechoic nodules (trunks and/or divisions) surrounded by a hyper-reflective fascial sheath, superficial and lateral to the round

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pulsating hypoechoic subclavian artery. All blocks were performed by the same supervised anesthesia resident. A 50-mm, 22-gauge insulated needle (PAJUNK, Uniplex NanoLine) was attached to the nerve stimulator (Xavant technology, Netherland), and then introduced lateral to the ultrasound probe, and parallel to the long axis of the probe, in the same plane as the ultrasound beam Once the needle penetrated the brachial plexus sheath and its tip was positioned among the nerves, the nerve stimulator was turned on and set to deliver a 1.0 mA current at 1 Hz frequency and 0.1 ms of pulse width. The current was decreased slowly when motor responses in the biceps or triceps were obtained. The tip of the needle was considered sufficiently close to the plexus when the muscle responses remained visible at 0.5 mA. After a negative aspiration the local anesthetic was injected at the site for over three to five minutes. Local anesthetic dispersion at the time of injection was seen by ultrasound. If the spread did not reach some part of the plexus, the needle tip position was readjusted to produce a suitable distribution of anesthetic.

Evaluation of the sensory and motor blocks was performed every minute after administration of the local anesthetic. The sensory block was quantified as: 0 = Anesthesia (no sensation), 1 = Analgesia (decreased [dull] sensation), and 2 = no block (normal sensation), by using the pinprick test and comparing with the contralateral limb. The time elapsed from the injection to the onset of analgesia in the central sensory region of each of the main peripheral nerves (ulnar, radial, medial, and musculocutaneous) was taken as time of onset of the sensory block.

The motor block was evaluated by assessing the flexion and extension of the forearm, opposition of the thumb and second digit, and opposition of the thumb and fifth digit. It was scored as follows: 0 = complete block (no muscle activity). 1 = partial block (decreased muscle activity), and 2 = no block (normal muscle activity), when compared with the contralateral limb. A score of 0 was taken as a complete motor block and the interval between the injection and block completion was considered as the onset of the motor block.

For patients in whom block success was not obtained 30 minutes after injection of the local anesthetic or the patient complained of pain at the surgical site during surgery, a supplemental rescue nerve block was performed, and the patient was excluded from data analysis. The time when the patients experienced the first postoperative pain was considered to be the end of the sensory block,[16,17] and the time to transfer them from the Recovery Unit to the Orthopedic Ward.

After operation, the patients were familiarized with a 10-point Verbal Analog Scale (VAS) for pain that ranged from 0 = no pain to 10 = the worst imaginable pain. The VAS was assessed and recorded on arrival to the Recovery Unit, 30 minutes later, and one, six, 12, and 24 hours after the operation, by an anesthesiologist, who was not aware of the group of study drugs. Twenty-four hours after surgery, the patients were asked to rate their satisfaction with the pain relief by VAS between 0 = no pain and 10 = the worst pain experienced.

During postoperative recovery in the hospital, pain (VAS >4 or patient request for analgesic) was treated with pethidine 25 mg increments every 20 minutes, as needed, until VAS <3, with a maximum dose of 100 mg in three hours. The time to the first request for analgesic and the total pethidine dose were documented. The patients who needed more than the maximum dose were excluded from the study and treated with other analgesics.

Upon arrival to the Recovery Unit, the level of consciousness was assessed according to the following scale:

Grade 1: Awake and alert,
Grade 2: Responding to verbal stimulus,
Grade 3: Responding to mild physical stimulus,
Grade 4: Responding to moderate-or-severe physical stimulus.

The heart rate and noninvasive blood pressure were recorded before anesthesia (baseline), every 15 minutes after injection of local anesthetic in the Operation Room, upon arrival to the Recovery Unit, and 30 and 60 minutes later.

All statistical analyses were performed using the Statistical Package of Social Sciences (SPSS) version 19.0 (SPSS, Chicago, IL, USA). The categorical data were analyzed using the χ^2 test. Comprising of the parametric data was analyzed using the student's t-test. Descriptive statistics were expressed as mean ± standard deviation or number (percent in parentheses). The heart rate and blood pressure changes were analyzed by Multivariate Analysis of Variance. Time to first rescue analgesics and total dose of pethidine were compared using a Kaplan-Meier survival analysis, followed by a log-rank test. A p-value less than 0.05 was considered statistically significant.

RESULTS

Sixty subjects with a mean age of 31.2 ± 11.5 years (range 17-60 years) participated in this study. All patients were included in the final analysis [Figure 1].

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The demographic and operative data were similar between groups [Table 1].

No significant differences were noted between groups in the onset and duration of the motor and sensory blocks [Table 2].

Patient satisfaction with pain relief provided for surgery was rated as 7.30 ± 1.87 (mean ± SD) in the control group and 8.93 ± 1.01 in the ketamine group. This difference was statistically significant ($P < 0.001$).

Time of administration of the first dose of pethidine was significantly more in the ketamine group, but the total pethidine dose was less [Table 3, Figures 2 and 3].

Comparison of VAS between groups at various times, postoperatively, has been presented in Table 4. The most significant and highest VAS pain scores were found in the control group at all time points ($P < 0.05$).

The multivariate analysis did not show any significant differences between the groups in heart rate (HR) or mean arterial pressure (MAP) when they were recorded before anesthesia (baseline), every 15 minutes for 90 minutes after brachial plexus block, upon arrival to the Recovery Unit, or 30 and 60 minute later. The *p*-values for HR were 0.783, 0.747, 0.880, 0.624, 0.929, 0.431, 0.970, 0.221, 0.918, and 0.838, respectively, and for MAP were 0.779, 0.623, 0.711, 0.688, 0.737, 0.824, 0.208, 0.538, 0.874, and 0.729, respectively, [Figures 4 and 5].

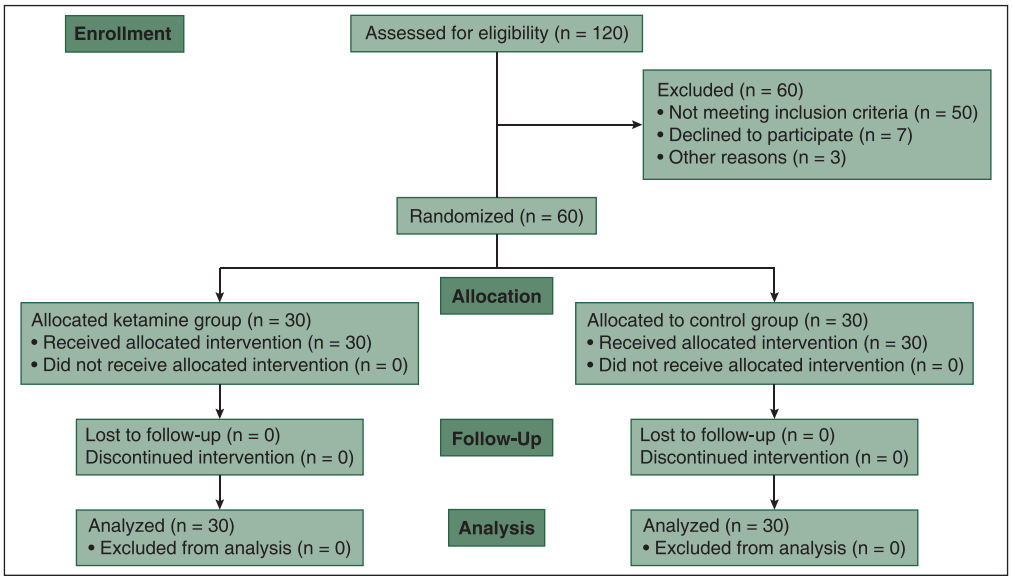

Figure 1: CONSORT flow diagram

Table 1: Demographic and operative data

Variable	Lidocaine	Lidocaine-Ketamine	*P*-Value
Weight [kg]	75.8 (±11.9)	77.5 (±10.3)	0.566
Age	31.7(±13)	30.3 (±9.9)	0.773
BMI [kg/m^2]	25.7 (± 3.6)	25 (±3.2)	0.413
Duration of operation [minutes]	70 (± 28)	77 (±27)	0.335
ASA [I/II]	23/7	25/5	0.209
Sex [male/female]	21/9	26/4	0.209
Type of operation [elbow/forearm/hand]	3/11/16	5/8/17	0.605

Data are expressed as mean ± SD or numbers, The statistical test used was student's t test for continuous data and Chi-Square test for qualitative data

Table 2: Onset and duration of sensory and motor blocks

Variable	Lidocaine	Lidocaine-Ketamine	*P* Value
Onset of sensory block (minutes)	7.1 (±2.55)	8.9 (±10.59)	0.385
Onset motor block (minutes)	12.37 (±3.69)	12.33 (±3.67)	0.973
Duration of sensory block (minutes)	189.77 (±22.43)	196.17 (±31.17)	0.365
Duration of motor block (minutes)	212.50 (±25.67)	221.83 (±28.60)	0.189

Data are expressed as mean ± standard deviation, The statistical test used was the student's t-test

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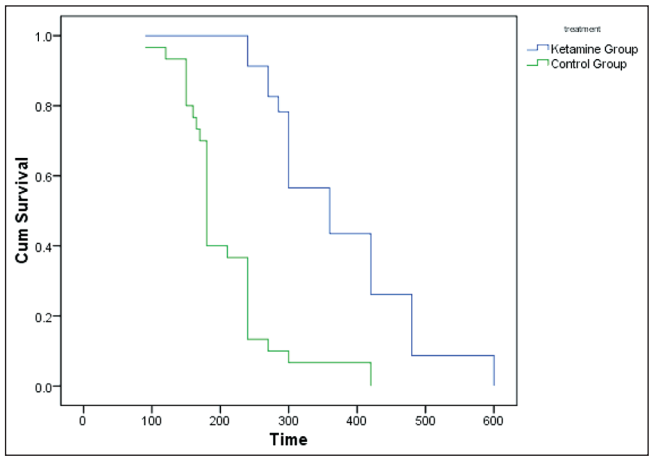

Figure 2: Kaplan-Meier survival curve describing the rescue time for the first dose of pethidine administration in the two groups

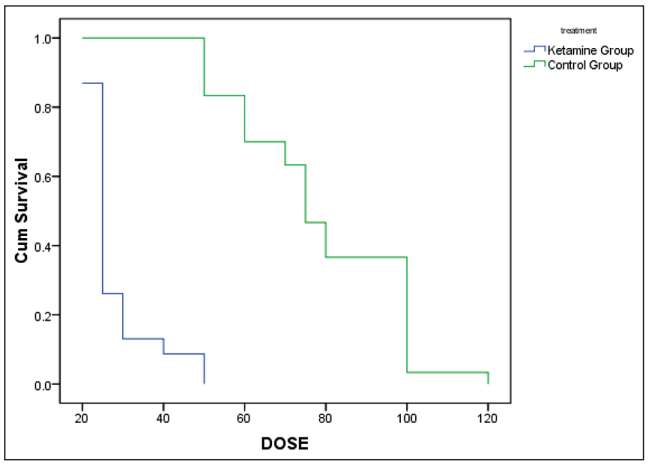

Figure 3: Kaplan-Meier survival curve describing the total dose of pethidine used in the two groups

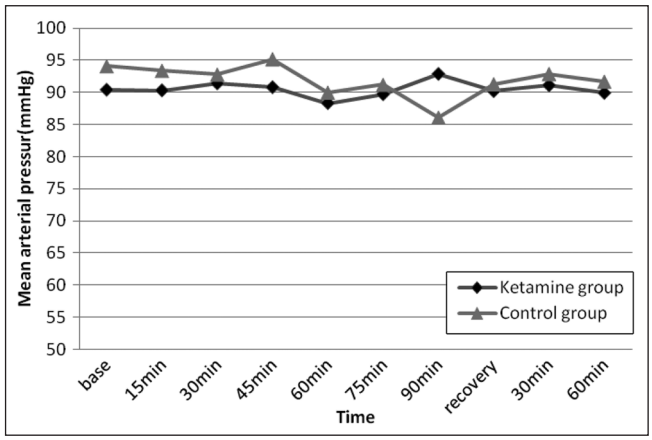

Figure 4: Mean arterial pressure during and after surgery. Mean arterial pressure was recorded before anesthesia (baseline), every 15 minutes for 90 minutes after brachial plexus block, upon arrival to the Recovery Unit, and 30 and 60 minutes later. There was no significant difference between the two groups

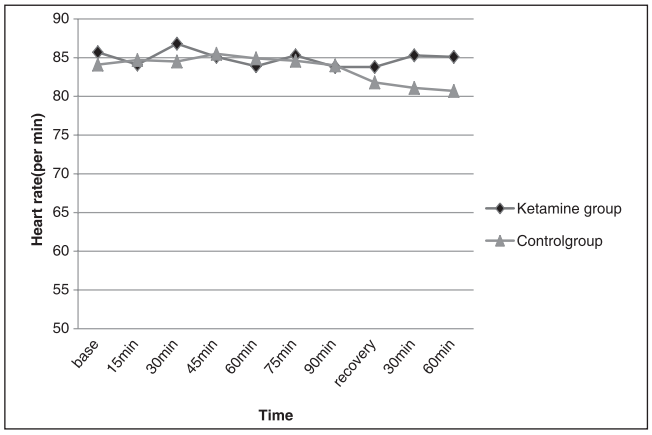

Figure 5: Heart rate during and after surgery. Heart rate were recorded before anesthesia (baseline), every 15 minutes for 90 minutes after brachial plexus block, upon arrival to the Recovery Unit, and 30 and 60 minutes later. There was no significant difference between the two groups

Table 3: Time of administration of the first dose and total dose of pethidine

Variable	Lidocaine	Lidocaine-Ketamine	*P* Value
Time of administration of first dose of pethidine (min)	207.5 (±73.6)	377.6 (±106.3)	<0.001
Total pethidine dose (mg)	169.1 (±44.8)	109.8 (±39.6)	<0.001

Data are expressed as mean ± standard deviation, The statistical test used was student's t test

Table 4: Pain scores (measured by VAS) in each treatment group at different time points after surgery

Variable	Lidocaine	Lidocaine-Ketamine	*P* Value
Arrival to recovery	1.350 (±0.989)	0.667 (±0.647)	0.002
30 minutes later	1.583 (±732)	0.767 (±668)	<0.001
One hour postoperatively	3.00(±1.287)	0.40(±0.770)	<0.001
Six hours postoperatively	3.77 (±1.382)	2.17 (±1.053)	<0.001
12 hours postoperatively	3.77 (±1.251)	2.43 (±1.251)	<0.001
24 hours postoperatively	3.00 (±1.203)	1.60 (±0.932)	<0.001

Data are expressed as mean ± standard deviation, The statistical test used was student's t test

All the patients in both groups were awake and alert on arrival to the Recovery Unit. Adverse effects occurred in seven patients (three patients had nausea and vomiting, two patients had agitation, and two patients had injection site ecchymosis) in the ketamine group and six patients (three patients had nausea and vomiting, one patient had agitation, and two patients had injection site ecchymosis) in the control group. There were no significant differences among the groups in the incidence of adverse-effects.

DISCUSSION

Our results suggest that the addition of ketamine to 1.5% lidocaine for ultrasound-guided brachial plexus block does not change the onset time and duration of sensory or motor block, but it can reduce postoperative pain.

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Ketamine is a phencyclidine derivative that has various central effects through the N-methyl-D-aspartate (NMDA) receptor. It is used for premedication, sedation, induction, and maintenance of general anesthesia. IV administration of ketamine provides significant postoperative analgesia through its central mechanism.[11] The role of a sub-anesthetic dose of ketamine as an anti-hyperalgesic or antiallodynic agent has recently gained increasing interest in pain management.[18,19]

Previous studies have indicated that the addition of ketamine (10-50 mg) to epidural bupivacaine or lidocaine prolongs the duration of regional anesthesia. They suggested that the enhancement of lidocaine epidural anesthesia by ketamine is more likely the result of the direct action of ketamine on the nerve root fibers rather than the action on the spinal cord.

Local anesthetic properties of ketamine were demonstrated by Dowdy *et al*.,[20] who reported that ketamine could produce reversible inhibition of the compound action potential in the stimulated frog sciatic nerve. Also, dogs injected with ketamine rapidly developed reversible segmental paralysis (with no alteration of the state of consciousness). The effect of ketamine on nerve conduction was confirmed by Weber *et al*.,[21] who reported that the subcutaneous infiltration of ketamine caused a loss of thermal and pain sensations for eight to ten minutes.

In our study the addition of ketamine to lidocaine solution did not improve the onset or duration of sensory or motor block. Similarly, Lee *et al*.,[14] showed that 30 mg of ketamine added to 30 ml of 0.5% ropivacaine in the brachial plexus block, did not improve the onset time or duration of sensory and motor block. However, contrary to the study of Lee *et al*., postoperative pain and need for analgesics in the ketamine group were decreased in our study. We do not have a clear explanation for this result. The analgesic effect could be the result of the local anesthetic effect of ketamine at the level of surgical trauma. Tverskoy *et al*.[13] showed that in patients whose wound were infiltrated with a solution of bupivacaine 0.5% and ketamine 0.3%, enhancement of the local anesthetic and analgesic effects of bupivacaine could not be explained by a central action of ketamine, and therefore, this effect was most likely peripheral.

Previously published studies suggest that the effect of ketamine is more likely to occur locally in an inflamed tissue, but not at the level of a nerve plexus distant from the surgical site. Ketamine has demonstrated a significant anti-inflammatory effect that significantly inhibits the early postoperative inflammatory response. It can act at different levels of inflammation, interacting with inflammatory cell recruitment, cytokine production, and inflammatory mediator regulation.[22,23]

Although we explained the peripheral effects for ketamine, the central mechanisms could not be rolled out in this study. The role of NMDAR in processing the nociceptive input could explain the analgesic properties of ketamine. The NMDAR is an excitatory glutamatergic receptor in the spinal and supraspinal sites involved in the afferent transmission of nociceptive signals. Other effects of ketamine that may contribute to its systemic analgesic behavior include, enhancement of the descending inhibition, interaction with other receptors, including the μ-opioid receptor, anti-inflammatory effects, and effect on the NMDAR at presynaptic sites.[24]

In contrast, in some studies, the addition of ketamine to local anesthetics has not improved the peripheral, regional, or local analgesia. Rahimzadeh *et al*.[15] compared the analgesic effects of peri-femoral nerve infusion of ketamine plus ropivacaine versus ropivacaine, after operation, in patients who underwent elective knee surgery for repairing the ACL, under spinal anesthesia. They reported that the addition of ketamine 1 mg/kg to 0.1% ropivacaine could not improve postoperative pain relief in the first 48 hours after the operation. Zohar *et al*.[25] reported that ketamine added to local bupivacaine did not enhance analgesia after wound infiltration following Cesarean section.

The addition of ketamine to local anesthetics failed to improve analgesia after intra-articular injection for knee arthroscopy[26] and its addition to bupivacaine for nerve block and wound infiltration after inguinal hernia repair did not improve postoperative pain relief significantly.[27]

The variable effect of ketamine in various studies probably came from the different ketamine concentrations and sites of injection. We administered 100-200 mg ketamine and it was more than what the previously mentioned studies had used and the complications and alterations in the level of consciousness were minor and transient.

Our study showed that ketamine decreased the severity of postoperative pain till 24 hours after surgery. As Tverskoy and colleagues[13] showed, the effect of ketamine on the inhibition of central sensitization explained the long-lasting analgesic effect of ketamine on postoperative pain. In the Tverskoy *et al*. study, the analgesic efficacy of ketamine when added to

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bupivacaine infiltration before inguinal hernia repair, by the same mechanism, lasted for one week after infiltration.

CONCLUSION

Our study showed that the addition of ketamine 2 mg/kg to lidocaine in the brachial plexus block did not improve the onset and duration of the sensory or motor block, but it decreased the postoperative pain and need for analgesics, without significant adverse effects. Therefore, it could be considered as an option to enhance the analgesic effects of the brachial plexus block.

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