ORIGINAL ARTICLE

Effectiveness of adding ketamine to ropivacaine infusion via femoral nerve catheter after knee anterior cruciate ligament repair

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Background: Elective knee surgery for repairing anterior cruciate ligament is usually associated with moderate to severe postoperative pain, and, therefore, selecting appropriate analgesia can considerably facilitate pain control and patient's discharge. This study was designed to compare the analgesic effectiveness of administration of ropivacaine or ropivacaine plus ketamine on pain control and improvement of muscle weakness after anterior cruciate ligament repair in adults. **Materials and Methods:** A double-blind randomized study which performed in Operating room and Sixty six patients with American Society of Anesthesiologists health status I to II that underwent elective knee surgery for repairing anterior cruciate ligament under spinal anesthesia were enrolled. Patients were randomly allocated to receive either ropivacaine 0.2% or an equivalent volume of ropivacaine 0.1% plus 1.0 mg/kg ketamine via continuous femoral block with pump infusion. The patients were familiarized with a 10-point verbal analog scale. Quadriceps muscle weakness and sedation score were assessed based on relevant scales. Parameters assessment were obtained from all patients immediately after PACU entrance, and postoperative assessment was performed at 4, 8, 12, 16, 20, 24, 30, 36, 42, and 48 h after the operation. **Results:** The data of 31 patients who received ropivacaine and of 33 patients in ketamine-ropivacaine group were eligible for analysis. Visual analogue scale (VAS) scores differed at various time points after surgery, with higher scores in patients who received concomitant ketamine and ropivacaine ($P < 0.05$). The degree of quadriceps muscle weakness was similar between the groups at the different time points. Patients in ropivacaine group rated better quality of pain control with appropriate sedation in comparison with the patients in ketamine/ropivacaine group. **Conclusion:** Our study shows that the addition of a ketamine 1 mg/kg to 0.1% ropivacaine via pump infusion after repairing anterior cruciate ligament could not improve pain control and muscle weakness.

Key words: Ketamine, pain, ropivacaine, visual analogue scale

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INTRODUCTION

Elective knee surgery for repairing anterior cruciate ligament (ACL) is usually associated with moderate to severe postoperative pain, and, therefore, selecting appropriate analgesia can considerably facilitate pain control and patient's discharge. In order to select the best drug regimen for postoperative analgesia while minimizing adverse events, some clinical researches have been designed to assess the efficacy of different drugs in various volumes, doses, and combinations.[1] On the other hand, recent efforts were targeted to improve postoperative pain relief via blocking pain pathways, especially via performing regional blocks.[2,3] Different drug regimens have introduced for regional pain management via catheters, and among these regimens, injection of ketamine has been shown to reduce postoperative pain, particularly in combination with local anesthetics.[4-7] One study has suggested that ketamine is a useful additive to bupivacaine for managing postoperative pain.[8] It has shown that administration of ketamine with the doses ranged 10-50 mg to epidural bupivacaine or lidocaine could increase the duration of regional anesthesia and postoperative analgesia.[8] This action can be mediated by interaction with a number of receptors like opioids, muscaranic, and N-methyl-D-aspartate (NMDA) receptors.[9-11] Because it has been already remained controversial whether adding ketamine peripherally to anesthetic agents can affect postoperative pain severity and motor block and muscle weakness grades, this double-blind randomized study was designed to compare the analgesic effectiveness of administration of ropivacaine or ropivacaine plus ketamine in the pain control and improvement of motor block after ACL repair in adults.

MATERIALS AND METHODS

Following ethics committee approval at the Tehran University of Medical Sciences and signing the written

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informed consent by the patients, 66 patients with American Society of Anesthesiologists (ASA) health status I to II, between 20-6- years, without history of substance abuse and allergy to local anesthetic and ketamine that underwent elective knee surgery for repairing ACL under spinal anesthesia at Rasoul-e-Akram Hospital between 2010 and 2011, were enrolled in this randomized, prospective, double-blinded study. Exclusion criteria were the patients didn't include in this study. follows: All of them were monitored by ECG, pulseoxymetry, heart rate, and non-invasive blood pressure measurement. Sedation was induced with midazolam (Exir daru, Iran), 1-2 mg intravenously. Spinal anesthesia was performed at L2-L3 or L3-L4 level by needle G25 whitacre (K-3 point type, Dr J) with bupivacaine 0.5% (Marcaine, Mylan) 2.5 ml plus 25 microgram fentanyl while the patient lying with the operating side downwards. All of the operations were performed by one surgeon. If the operation was extended more than usual time (120-150 minutes), the patient was excluded from study. After the operation, all patients were monitored in post-anesthesia care unit by standard monitoring, including non-invasive arterial blood pressure, heart rate, and pulse oximetry for femoral nerve block. Firstly, the pulse of femoral artery was determined on the junction with inguinal ligament. About 1.5 cm lateral and caudal to this point, nerve stimulator needle (Poly medic, 18 G, 1.30. 50 mm, Te me na SAS, EU) was advanced about 4 cm with 60° upward angle. Using the nerve stimulator instrument (Polymedic, Te me na SARL, EU), and with a current intensity of 2 mA, a frequency of 2 Hz, and an impulse width of 100 μs, contractions of quadriceps muscle was determined. Then, current intensity of the instrument was gradually decreased to 0.5 mA. The target point of needle was fixed if the responses were detected with the current intensity of 0.5 mA or lower, and then, after negative blood aspiration, a 0.3 mL/kg test dose of ropivacaine 0.2% was injected. Then, catheter was advanced through the needle and fixed via tunneling method and secured with transparent dressing. The implanted catheter was non-stimulant type, and all of nerve blocks were performed by one anesthetist. The pumps were filled by another person who was not aware of groups. Patients were selected by block randomization by the third person to receive either ropivacaine 0.2% (Naropine, AstraZenca) (G1) or an equivalent volume of ropivacaine 0.1% plus 1.0 mg/kg ketamine (Rotexmedica, Germany) G2 via pump infusion, and postoperative analgesia was performed using auto fuser pump (Ace Medical, Korea) and with the speed of 5 mL/hour continuous flow from the above-mentioned drugs.

After operation, the patients were familiarized with a 10-point verbal analog scale (VAS) ranged from 0 = no pain, up to 10 = the worse imaginable pain. VAS was measured at rest. Quadriceps muscle strength was measured by using a qualitative measurement using a 6-point numerical scale (MRC scale). Qualitative 6-point rating scales of quadriceps muscle strength (MRC) grades are as follow: 0 = No muscle action; 1 = Flicker of movement; 2 = Unable to overcome gravity; 3 = Able to overcome gravity; 4 = Able to overcome gravity and moderate resistance; and 5 = Assessor unable to manually overcome the muscle power (10). Sedation was also graded using the Ramsay sedation scale, where 1 = Patient was anxious, agitated, or restless; 2 = Patient was co-operative, oriented, and tranquil; 3 = Patient responds to command only; 4 = Patient exhibits brisk response to light glabellar tap or loud auditory stimulus; 5 = Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus; and 6 = Patient exhibits no response.[12] Above mentioned parameters assessment were obtained from all patients in PACU, and postoperative assessment of these parameters was performed and recorded at 4, 8, 12, 16, 20, 24, 30, 36, 42, and 48 h after the operation by an anesthesiologist who was not aware of the group of study drugs. In case of incomplete pain control, the position of catheter tip was checked with ultrasound machine (Micro Maxx, Sonosite, USA), and if the catheter was not in perineural region, the patient was excluded from study.

For breakthrough pain and VAS > 3, intravenous meperidine 0.3 mg/kg was used. In the postoperative days and at selected times, if patients had a MRC < 3 or an inadequate sense of joint position, they were not allowed to walk but followed a training program in bed. Probable side-effects such as nausea, vomiting were recorded also.

Results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Categorical variables were compared using Chi-square test or Fisher's exact test when more than 20% of cells with expected count of less than five were observed. Quantitative variables were also compared with Mann-Whitney U test. Statistical significance was determined as a $P \leq 0.05$. All statistical analysis was performed using SPSS software (version 13.0, SPSS Inc., Chicago, Illinois). Because of importance of VAS as the first outcome in this study, sample size was calculated on this base. Considering the previously done studies, the mean of VAS in ropivacaine alone cases were presumed 3 with SD = 1.2(σ = 1.2). After adding ketamine, we expected to have a mean decline in VAS scale about 1. The sample size with assumption of $\alpha = 0.05$, $\beta = 0.1$ (power = 90%) calculated from this formula:

$$2N = \frac{4\left(Z1-\frac{\alpha}{2}+Z1-\beta\right)^2\sigma^2}{\delta 2}$$

N = 30 in each group was calculated.

RESULTS

The data of 31 patients in G1 (Two patients were not entered into the study because of lack of operation) and of 33 patients in G2 were eligible for analysis. There was no significant intergroup difference with regard to male to female ratio (0.74 versus 0.82, $P = 0.461$) and mean age (31.5 ± 8.2 years versus 32.6 ± 8.9 years, $P = 0.626$). There were also no differences between the groups in baseline blood pressure and heart rate variables. The mean duration of surgery was 118 ± 2.2 minutes, and mean duration of spinal anesthesia was 136 ± 2.4 minutes ($P = 0.23$ and 0.34).

The pain scores on recovery room and in the first 48 hours postoperatively are shown in Table 1. VAS scores in PACU entrance time were comparable in the two groups, while these scores differed at various time points after surgery, with higher scores in patients who received concomitant ketamine and ropivacaine ($P < 0.05$). Also, the trend of pain severity changes in patients received ropivacaine and those who were administered concurrent ketamine and ropivacaine was not different within 48 hours after operation [Figure 1] ($P = 0.714$).

The grade of quadriceps muscle strength of the operated knee was lower in G1, and more patients experienced muscle weakness in this group, but it was not statistically significant between groups [Table 2]. Intramuscular meperidine needed in all patients in the G2, but only seven patients (22.5%) of G1 needed it, and administration of this drug was significantly higher in those who were in G2 (69.2 ± 32.0 mg versus 31.4 ± 14.6 mg, $P = 0.010$). All of implanted catheters were in correct position under sonography view. Patients received ropivacaine rated better sedation score than who received ketamine/ropivacaine, which was statistically significant [Table 3]. (2.0 ± 0.10 in ropivacaine group versus 1.20 ± 0.15 in ketamine/ropivacaine group, $P < 0.001$).

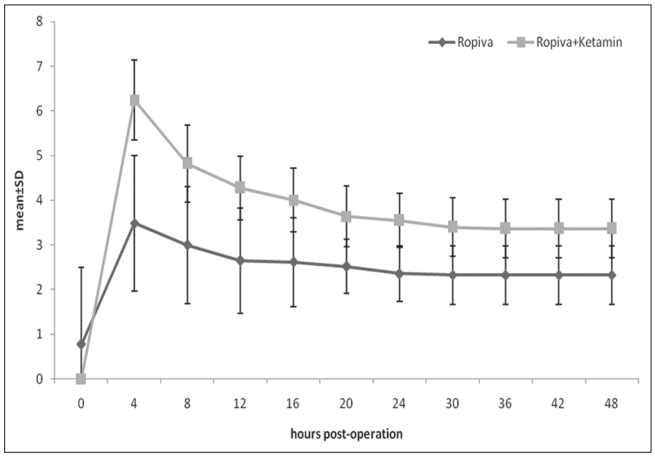

Figure 1: Trend of pain severity changes in patients received ropivacaine or concurrent Ketamine and ropivacaine (P value = 0.714)

DISCUSSION

In recent years, several studies have indicated the beneficial effects of femoral nerve block on acute postoperative pain control and rehabilitation programs after knee surgeries.[10] Actually, the main protocol for ACL surgery

Table 1: Distribution of postoperative pain severity based on visual analogue scale

Time point	Isolated ropivacaine (*n*=31)	Ketamine and ropivacaine (*n*=33)	*P* value
PACU entrance	0.77±2.49	0.00±0.00	0.090
4-hour after surgery	3.48±0.88	6.24±1.52	<0.001
8-hour after surgery	3.00±0.85	4.81±1.30	<0.001
12-hour after surgery	2.64±0.70	4.27±1.17	<0.001
16-hour after surgery	2.61±0.71	4.00±1.00	<0.001
20-hour after surgery	2.51±0.67	3.63±0.60	<0.001
24-hour after surgery	2.35±0.60	3.54±0.61	<0.001
30-hour after surgery	2.32±0.65	3.39±0.65	<0.001
36-hour after surgery	2.32±0.65	3.36±0.65	<0.001
42-hour after surgery	2.32±0.65	3.36±0.65	<0.001
48-hour after surgery	2.32±0.65	3.36±0.65	<0.001

PACU=Post Anesthesia Care Unit

Table 2: Distribution of postoperative grading of quadriceps muscle strength according to MRC

Time point (MRC<3)	Isolated ropivacaine (*n*=31)	Ketamine and ropivacaine (*n*=33)	*P* value
PACU entrance	22 (71.0)	16 (48.4)	0.067
4-hour after surgery	22 (71.0)	16 (48.4)	0.067
8-hour after surgery	21 (64.5)	16 (48.4)	0.119
12-hour after surgery	19 (61.3)	16 (48.4)	0.196
16-hour after surgery	19 (61.3)	15 (45.4)	0.126
20-hour after surgery	19 (61.3)	15 (45.4)	0.126
24-hour after surgery	19 (61.3)	15 (45.4)	0.126
30-hour after surgery	19 (61.3)	15 (45.4)	0.126
36-hour after surgery	19 (61.3)	15 (45.4)	0.126
42-hour after surgery	19 (61.3)	15 (45.4)	0.126
48-hour after surgery	19 (61.3)	15 (45.4)	0.126

MRC=Medical Research Council scale ; PACU=Post Anesthesia Care Unit

Table 3: Distribution of postoperative sedation score

Time point	Isolated ropivacaine (*n*=31)	Ketamine and ropivacaine (*n*=33)	*P* value
4-hour after surgery	2.08±0.01	1.14±0.02	<0.001
8-hour after surgery	1.90±0.11	1.11±0.20	<0.001
12-hour after surgery	1.80±0.12	1.27±0.17	<0.001
16-hour after surgery	2.01±0.11	1.00±0.10	<0.001
20-hour after surgery	2.01±0.2	1.33±0.2	<0.001
24-hour after surgery	1.95±0.20	1.34±0.21	<0.001
30-hour after surgery	2.02±0.25	1.40±0.21	<0.001
36-hour after surgery	2.02±0.25	1.36±0.10	<0.001
42-hour after surgery	2.0±0.05	1.40±0.05	<0.001
48-hour after surgery	2.0±0.15	1.40±0.15	<0.001

is to move the operated knee as soon as possible, in order to reduce the postoperative complications and hospital costs and to accelerate the time of discharge. The current study focused on the first 48 hours after knee surgery for repairing ACL, during which many patients experience the most peak pain level. We tried to compare postoperative analgesic effects with peri-femoral nerve infusion of ketamine and ropivacaine versus ropivacaine. Continuous femoral analgesia with 0.2% ropivacaine could cause favorable analgesia, but muscle weakness and inability to perform voluntarily knee movements could cause patient dissatisfaction. In this study, lower concentration of ropivacaine was used in order to decrease the above mentioned side-effects. Ketamine which is a strong NMDA antagonist and acts on sodium channels like a local anesthetic was used as an adjuvant for this purpose. Our clinical study showed no pain relief enhancement within 48 hours after the addition of ketamine to ropivacaine; on the other hand, this analgesia protocol led to more reported pain complaints in these patients, and patients in this group could not move their knees and perform voluntarily exercise due to incomplete pain control via pump infusion. Meperidine was used for all of them.

But, some previous studies observed lower pain scores over three days when patients received preoperative small-dose ketamine after starting knee arthroplasty with epidural or general anesthesia,[7] and in some others, small-dose ketamine epidurally combined with bupivacaine failed to improve postoperative pain relief after knee arthroplasty with epidural anesthesia.[13]

Some evidences have supported the short-term use of ketamine for relieving neuropathic and nociceptive pain; however, there are some other conflicting evidences against its consumption for chronic neuropathic pain because of its related notable side-effect profile.[14] Recent concern has been expressed about neurotoxicity and neuro-side-effects after the use of ketamine, because myelopathy and neurological injuries has been reported with intrathecal injection of this agent, particularly with larger dosages.[15-17] The variable effects of ketamine probably come from the different ketamine concentrations. It has been suggested that the peri-incisional use of 0.3-0.5% ketamine combined with local anesthetic is maximally effective for wound analgesia, so peripherally acting mechanism has mentioned for this drug.[18,19] In Argiriadou *et al.*'s study in 2011, the effects of intravenous infusion of S(+) ketamine were evaluated on post-thoracotomy pain in patients receiving ropivacaine infusion via paravertebral catheters in comparison with parecoxib injection, and their study showed that postoperative paravertebral ropivacaine combined with intra-operative S(+)-ketamine provided better early postoperative pain relief than ropivacaine and peri-operative parexocib or ropivacaine alone.[20] In our survey, ketamine was injected peripherally with the dose of 1 mg/kg that seems to be higher than peripherally administered dosages in other studies. Even, it has been shown that 30 mg ketamine is a relatively small dose, there might be resulted in many detectable adverse effects after injection.[11] It seems that the addition of ketamine infusion with the dose of 1 mg/kg to 0.1% ropivacaine might led to incomplete pain control, and higher concentrations of the used drugs are recommended for future studies.

This study also suggests that 1 mg/kg ketamine added to ropivacaine in the nerve block does not improve the duration of motor block and quadriceps weakness. Similarly, Lee *et al.* showed that adding 30 mg of ketamine not only did not improve sensory and motor block in interscalene block, but it caused a relatively high incidence of adverse effects.[11] On the other hand, our study did not even find a trend toward shorter onset of quadriceps weakness when ketamine was added to ropivacaine. Therefore, it seems that ketamine infusion with the selected dosage does not shorten the onset time of block induced by local anesthetics, probably because of the lack of effective drug concentration at the site of injection; so, it has been suggested by the authors of this article that bolus injection of such dosage might be probably more effective. In addition, it has been observed that the effect of ketamine might be different when injected at the level of inflamed tissue compared with the normal tissue site.[11]

Limitations of this study

Totally, more research is needed to better ascertain postoperative efficacy of ketamine to pain relief as well as motor block and muscle weakness shortening besides its side-effects. Another limitation of this study is to design it in three groups and via ultrasound guidance and with bolus injection of ketamine and author recommend to do it by researchers in the future considering the above mentioned points.

CONCLUSION

In summary, our study shows that the addition of a ketamine 1 mg/kg to 0.1% ropivacaine via continuous femoral block pump infusion after repairing anterior cruciate ligament could not improve pain control and muscle weakness.

REFERENCES

1. Ayoglu H, Altunkaya H, Bayar A, Turan IO, Ozer Y, Ege A. The effect of intraarticular combinations of tramadol and ropivacaine with ketamine on postoperative pain after arthroscopic meniscectomy. Arch Orthop Trauma Surg 2010;130:307-12.
2. Yaksh TL, Hua XY, Kalcheva I, Nozaki-Taguchi N, Marsala M. The spinal biology in humans and animals of pain states generated by persistent afferent input. Proc Natl Acad Sci USA 1999;96:7680-6.

3. Himmelseher S, Ziegler-Pithamitsis D, Argiriadou H, Martin J, Jelen-Esselborn S, Kochs E. Small-dose S(+)-ketamine reduces postoperative pain when applied with ropivacaine in epidural anesthesia for total knee arthroplasty. Anesth Analg 2001;92:1290-5.
4. Webb AR, Skinner BS, Leong S, Kolawole H, Crofts T, Taverner M, *et al*. The addition of a small-dose ketamine infusion to tramadol for postoperative analgesia: A double-blinded, placebo-controlled, randomized trial after abdominal surgery. Anesth Analg 2007;104:912-7.
5. Adam F, Chauvin M, Du Manoir B, Langlois M, Sessler DI, Fletcher D. Small-dose ketamine infusion improves postoperative analgesia and rehabilitation after total knee arthroplasty. Anesth Analg 2005;100:475-80.
6. Aida S, Yamakura T, Baba H, Taga K, Fukuda S, Shimoji K. Preemptive analgesia by intravenous low-dose ketamine and epidural morphine in gastrectomy: A randomized double-blind study. Anesthesiology 2000;92:1624-30.
7. Wong CS, Lu CC, Cherng CH, Ho ST. Pre-emptive analgesia with ketamine, morphine and epidural lidocaine prior to total knee replacement. Can J Anaesth 1997;44:31-7.
8. Abdel-Ghaffar ME, Abdulatif M, al-Ghamdi A, Mowafi H, Anwar A. Epidural ketamine reduces postoperative epidural PCA consumption of fentanyl/bupivacaine. Can J Anaesth 1998;45:103-9.
9. Petrenko AB, Yamakura T, Baba H, Shimoji K. The role of N-methyl-D-aspartate (NMDA) receptors in pain: A review. Anesth Analg 2003;97:1108-16.
10. Paauwe JJ, Thomassen BJ, Weterings J, van Rossum E, Ausems ME. Femoral nerve block using ropivacaine 0.025%, 0.05% and 0.1%: Effects on the rehabilitation program following total knee arthroplasty: A pilot study. Anesthesia 2008;63:948-53.
11. Lee IO, Kim WK, Kong MH, Lee MK, Kim NS, Choi YS, Lim SH. No enhancement of sensory and motor blockade by ketamine added to ropivacaine interscalene brachial plexus blockade. Acta Anaesthesiol Scand 2002;46:821-6.
12. Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxolone-alphadalone. BMJ 1974;2:656-9.
13. Weir PS, Fee JP. Double-blind comparison of extradural block with three bupivacaine-ketamine mixtures in knee arthroplasty. Br J Anaesth 1998;80:299-301.
14. Cohen SP, Liao W, Gupta A, Plunkett A. Ketamine in pain management. Adv Psychosom Med 2011;30:139-61.
15. Karpinsky N, Dunn J, Hansen L, Masliah E. Subpial vacuolar myelopathy after intrathecal ketamine: Report of a case. Pain 1997;73:103-5.
16. Errando CL, Sifre C, Moliner S, Valía JC, Gimeno O, Mínguez A, *et al*. Subarachnoid ketamine in swine: Pathological findings after repeated doses-acute toxicity study. Reg Anesth Pain Med 1999;24:146-52.
17. Yang CY, Wong CS, Chang JY, Ho ST. Intrathecal ketamine reduces morphine requirements in patients with terminal cancer pain. Can J Anaesth 1996;43:379-83.
18. Weber WV, Jawalekar KS, Jawalekar SR. The effect of ketamine on the nerve conduction in isolated sciatic nerves of the toad. Neurosci Lett 1975;1:115-20.
19. Tverskoy M, Oren M, Vaskovich M, Dashkovsky I, Kissin I. Ketamine enhances local anesthetic and analgesic effects of bupivacaine by peripheral mechanism: A study in postoperative patients. Neurosci Lett 1996:215:5-8.
20. Argiriadou H, Papagiannopoulou P, Foroulis CN, Anastasiadis K, Thomaidou E, Papakonstantinou C, *et al*. Intraoperative infusion of S(+)-ketamine enhances post-thoracotomy pain control compared with perioperative parecoxib when used in conjunction with thoracic paravertebral ropivacaine infusion. J Cardiothorac Vasc Anesth 2011;25:455-61.

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