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The comparison of intraarticular morphine–bupivacaine and tramadol–bupivacaine in postoperative analgesia after arthroscopic anterior cruciate ligament reconstruction

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Abstract
Purpose To compare intraarticular morphine–bupivacaine and tramadol–bupivacaine as postoperative analgesics in patients undergoing arthroscopic anterior cruciate ligament (ACL) reconstruction.
Methods A randomized, double blind, controlled trial study of 60 ASA I–II patients undergoing arthroscopic ACL reconstruction was performed under general anesthesia. Patients were randomly allocated into three groups. The MB group ($n = 20$) received 10 mg morphine and 0.5% bupivacaine; the TB group ($n = 20$) received 100 mg tramadol and 0.5% bupivacaine; and the control group ($n = 20$) received isotonic saline intraarticularly in a total volume of 20 ml after the operation. Postoperative pain was assessed with visual analogue scale (VAS) at 0, 30, 60, 90 min and 2, 4, 6, 12, 24 h being at rest. Analgesic duration as defined was the time of first request for analgesics, the first 24 h analgesic consumption, time to unassisted ambulation, discharge time and incidence of side effects were also evaluated.
Results The VAS scores at 30, 60, 90 min and 2, 4, 12, 24 h were significantly less in the MB and TB groups in comparison with the control group ($P < 0.05$); VAS scores also decreased significantly in the MB group compared to the TB group at 2, 4 and 24 h ($P < 0.05$). Analgesic duration was longer and analgesic consumption was substantially less in the MB group ($P < 0.05$). Moreover, unassisted ambulation time and discharge time were significantly shorter in the MB group than the TB and control groups ($P < 0.05$). Side effects were similar among the groups.
Conclusions Intraarticular morphine–bupivacaine provides effective pain relief, longer analgesic duration, less analgesic requirement, shorter unassisted ambulation and discharge time were compared with intraarticular tramadol–bupivacaine after ACL reconstruction arthroscopy.
Level of evidence I.

Keywords Intraarticular analgesia · Morphine · Bupivacaine · Tramadol · Anterior cruciate ligament reconstruction

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Introduction

Knee arthroscopy under general anesthesia is one of the most common surgical procedures being performed in case of knee injuries and disorders and is often associated with postoperative pain. Intraarticular (IA) local analgesia has been widely used for management of pain after the arthroscopic knee surgery. Different adjuvant drugs, including opioids, non-steroidal anti-inflammatory drugs, ketamine, clonidine, bupivacaine and neostigmine, have been used in IA to improve pain relief and duration and quality of analgesia after knee arthroscopy [3, 7, 10, 26].

Morphine as an opioid and bupivacaine as a local anesthetic are both drugs that are used frequently in simple or compound form into the intraarticular space of the knee joint after arthroscopic surgery [4, 9, 15, 24]. The analgesic effect of morphine is delayed onset (about 2 h after injection); but it considerably has long duration (as long as 48 h postoperatively), because morphine has lower lipid solubility, which accounts for its slow rate of absorption into the circulation from a low blood flow to the articular area [16]. Also, it has been proposed that glucoronidation of morphine intraarticularly may produce morphine-6-glucoronide which has a longer half-life that may account for the more prolonged effect [17].

Bupivacaine has relatively high lipophilicity which is responsible for its faster uptake into the circulation and its removal from the joint thus suggesting that bupivacaine is immediate onset of action but only of short duration (2–3 h) [31].

Tramadol is a weak (selective μ receptor) opioid agonist and there are a few studies investigating the analgesic effects of intraarticular administration of it after arthroscopic knee surgery [1, 2, 20, 23]. Recently, Zeidan et al. [38] indicated that intraarticular admixture of tramadol with bupivacaine provides a pronounced prolongation postoperative analgesia in patients undergoing arthroscopic knee surgery; the same results have also been observed in intraarticular tramadol plus periarticular bupivacaine combination following arthroscopic outpatient partial meniscectomy surgery [8].

Reconstruction of the anterior cruciate ligament (ACL) is usually associated with postoperative sever pain. Several studies have suggested ways to resolve the problem, some of which are IA injection of anesthetic and narcotic compounds [11, 32]. However, no study to date has been conducted to compare using IA combination of morphine–bupivacaine and tramadol–bupivacaine in patients undergoing ACL reconstruction with arthroscopic knee surgery.

In this randomized, double blind, controlled trial study, the primary aim was to compare the analgesic effects of IA 10 mg morphine–bupivacaine 0.5% and 100 mg tramadol–bupivacaine 0.5% with placebo injected into the knee for postoperative analgesia in patients undergoing arthroscopic ACL reconstruction with visual analogue scale (VAS) [35]. The secondary aims were duration of analgesia which as defined was the time of first request for analgesics, 24 h following consumption of it, the time of unassisted ambulation, the time to discharge and the incidence of side effects such as nausea, vomiting, pruritus and respiratory depression in patients. It was hypothesized that there are different analgesic effects between IA morphine–bupivacaine and tramadol–bupivacaine in arthroscopic ACL reconstruction.

Materials and methods

After approval of the study by the research ethics committees in Shahid Sadoughi University of Medical Sciences, written informed consents were obtained from 60 male patients. The patients with ASA physical status of I–II, aged between 16 and 37 and weight between 57 and 85 kg, were scheduled to undergo elective arthroscopic ACL reconstruction. Exclusion criteria were allergy and contraindication to study drugs, long-term treatment with analgesics, consumption of analgesics or non-steroid anti-inflammatory drugs before and during of surgery, the need for postoperative intraarticular drainage, traumatic injury to the knee and other knee disorders.

Before the operation, all patients received instructions for using 100 mm VAS scores (subjective measurement, with 0: no pain, to 100: worst pain possible) and the mean of pain scores was 12.8 mm preoperatively. Premedication was midazolam 0.03 mg/kg intravenously, 30 min before the start of anesthesia. Standard monitoring techniques were used including electrocardiography, non-invasive blood pressure and pulse oximetry. All operations were performed under general anesthesia being induced with fentanyl (1–1.5 μg/kg) and thiopanthal (3–4 mg/kg) intravenously (IV). Tracheal intubation was facilitated with atracurium (0.6 mg/kg), and anesthesia was continued with 0.8–1.2 minimum alveolar concentration (MAC) isofluran and O_2 30% and N_2O 70% which were breathed in. No other supplementary analgesic medications were administered during surgery. A thigh pneumatic tourniquet at a pressure of 300 mmHg was applied on the same side of surgery to all patients. One surgeon performed all surgical procedures using a standard surgical technique.

When the surgical procedure was completed, patients were assigned into 3 groups (20 patients for each) by using a randomized number table. The MB group received 10 mg morphine sulfate (Darou Pakhsh Pharmaceutical Co. Iran) and 0.5% bupivacaine (Mylan Pharmaceutical Co. France); the TB group received 100 mg tramadol hydrochloride (Exir Pharmaceutical Co. Iran) and 0.5% bupivacaine and the control group received 20 ml of isotonic saline intra-articularly in a double-blinded randomized study. The volume of the injection was standardized at 20 ml. At the end of the operation, the study drugs were injected in the patient's knee joint through the arthroscopic portal by the surgeon who was blinded to the drugs and the tourniquet was released 10 min after drug injections. No intraarticular drain was used.

After the end of anesthesia, patients were transferred to the postanesthesia care unit. Pain was assessed with VAS by questioning the patients at 0, 30, 60, 90 min, 2, 3, 4, 6, 12 and 24 h after the operation, only at rest. The complaint of pain was eliminated by morphine IV with patient

controlled analgesia (Ace Medical Co. Korea) set up to deliver incremental doses of 1 mg morphine and lockout of 15 min with no background infusion. Also, the time for first analgesic use, the first 24 h of analgesic consumption and the occurrence of side effects such as nausea, vomiting, pruritus and respiratory depression (rate <10 breaths/min) were all noted for each patient.

Patients were discharged when they were oriented to time and place, had stable vital signs, minimal or no pain, absence of nausea, vomiting and other side effects and ambulating with or without the assistance of crutches; discharge time was defined as the time from the end of the surgery until the patient meets discharge conditions. The time of ambulation without any assistance also was reported by patients. Demographic data including age and weight of the patients, right or left knees, and duration of anesthesia were recorded for each patient.

Statistical analysis

As an initial comparison in intraarticular injection of morphine–bupivacaine and tramadol–bupivacaine for post-operative analgesia in patients undergoing arthroscopic ACL reconstruction, we conducted a pilot study on 14 patients; on the basis of VAS at 24 h (the MB group: 20.8 ± 4.8, the TB group: 24.7 ± 4.1) the sample size calculation turned to be 16 patients per group but we set sample size at 20, as the initial study. Power analysis was 0.8, and α set was at 0.05. Statistical analysis was performed using the SPSS 15.0 software, and $P < 0.05$ was accepted to be statistically significant. Data were presented as mean ± SD. The data between the groups were analyzed by one-way ANOVA test and for comparing the two groups, Tukey HSD test was used.

Results

Demographic and anesthesia data are presented in Table 1. No significant difference was found among the three groups with respect to age, weight, knees and duration of anesthesia. No differences were found among the groups in the preoperative VAS scores. Except 0 min and 6 h after operation, at all times the VAS scores were significantly less in the MB and TB groups in comparison with the control group ($P < 0.05$). Also, VAS scores decreased significantly in the MB group compared to the TB group at 2, 4 and 24 h after operation ($P < 0.05$). In total VAS scores in 24 h, there was a notable difference only between the cases groups and the control group ($P < 0.05$) (Table 2).

The percentage of patients in the MB group requiring rescue analgesia was 45% which was significantly less than the percentage of patients in the both TB group (75%) and control group (100%). Duration of analgesia was longer, and the first 24 h analgesic consumption was substantially less in the MB group compared to other groups ($P < 0.05$). Moreover, discharge time and time of unassisted ambulation were significantly shorter in the MB group than the TB and control groups ($P < 0.05$) (Table 3).

In assessing the side effects, none of the patients had respiratory depression and there was no significant difference between the groups in terms of nausea, vomiting and pruritus (Table 4).

Discussions

The most important finding of the present study was IA morphine–bupivacaine provides effective pain relief, a longer duration of analgesia, a decrease in the first 24 h analgesic consumption, shorter unassisted ambulation and discharge time than tramadol–bupivacaine after ACL reconstruction arthroscopy.

Opioids analgesia has been associated with the activation of opioid receptors in the central and peripheral nervous system; however, peripheral opioids receptors (μ, δ and κ) are activated only in the presence of inflamed tissue in synovial membrane of the knee joint [21, 29, 30]. On the other hand, the peripheral activity of morphine is mediated by progressive changes on the peripheral sensory nerve terminals that stimulate the axonal transport of opioids receptors and results in antinociception [13, 22, 34, 37]. In this regard, Stein et al. [28] showed that small doses (1 mg) of IA morphine significantly reduces postoperative pain after arthroscopic knee surgery and is neutralized by IA naloxone thus confirming a local analgesic effect of morphine. Morphine can reduce local post-traumatic

Table 1 Demographic and anesthesia data

	Group MB ($n = 20$)	Group TB ($n = 20$)	Control group ($n = 20$)
Age (years)	25.3 ± 4.7	25.3 ± 4.1	25.2 ± 4.3
Weight (kg)	70.1 ± 6.9	72.0 ± 6.4	71.0 ± 6.9
Gender (M/F)	20/0	20/0	20/0
Knee (left/right)	9/11	11/9	9/11
Duration of anesthesia (min)	62.1 ± 4.4	62.3 ± 5.1	63.9 ± 4.7

Table 2 Pain scores (VAS, 0–100 mm), presented as mean ± SD

	Group MB ($n = 20$)	Group TB ($n = 20$)	Control group ($n = 20$)	P value
Preoperative				
VAS	11.0 ± 6.1	13.1 ± 7.2	14.1 ± 5.9	n.s.[a]
				n.s.[b]
				n.s.[c]
Postoperative				
VAS 0 min	28.8 ± 4.6	28.3 ± 4.7	31.4 ± 5.4	n.s.[a]
				n.s.[b]
				n.s.[c]
VAS 30 min	33.7 ± 5.3	32.4 ± 3.6	38.9 ± 4.9	0.003[a]
				0.000[b]
				n.s.[c]
VAS 60 min	19.4 ± 4.5	20.6 ± 6.1	47.5 ± 3.6	0.000[a]
				0.000[b]
				n.s.[c]
VAS 90 min	26.5 ± 4.5	27.6 ± 5.0	60.1 ± 5.2	0.000[a]
				0.000[b]
				n.s.[c]
VAS 2 h	19.2 ± 4.9	32.5 ± 5.8	36.5 ± 2.8	0.000[a]
				0.024[b]
				0.000[c]
VAS 4 h	25.6 ± 4.8	39.2 ± 5.9	52.7 ± 4.1	0.000[a]
				0.000[b]
				0.000[c]
VAS 6 h	41.9 ± 6.2	42.0 ± 11.5	40.0 ± 2.9	n.s.[a]
				n.s.[b]
				n.s.[c]
VAS 12 h	43.0 ± 9.6	47.7 ± 7.3	56.9 ± 3.4	0.000[a]
				0.001[b]
				n.s.[c]
VAS 24 h	20.1 ± 3.8	25.5 ± 3.1	36.8 ± 3.1	0.000[a]
				0.000[b]
				0.000[c]
Total VAS in 24 h	28.7 ± 9.1	32.8 ± 8.6	44.5 ± 10.1	0.004[a]
				0.036[b]
				n.s.[c]

[a] Difference between group MB and control group

[b] Difference between group TB and control group

[c] Difference between group MB and TB

inflammation through actions in leukocytes, inhibition of bradykinin formation or inhibition of plasma extravasation [6, 14, 36].

Bupivacaine is a local anesthetic drug that produces its effects through inhibition of the generation and/or dissemination of action potentials at the neuronal membrane and a resulting blockade of afferent nociceptive barrage. Since Khoury et al. [19] recommended that a satisfactory IA analgesia should be used in the form of the combination of both morphine and bupivacaine, IA bupivacaine and/or intraarticular morphine have been widely used for the management of pain after arthroscopic knee surgery [3, 4, 9, 15, 24]. Eroglu et al. [12] indicated that administration of 5 mg morphine and 20 ml of 0.25% bupivacaine intraarticularly provides better pain relief and shorter discharge time without increasing the side effects than placebo for an outpatient arthroscopic knee surgery performed under a low dose of spinal anesthesia. Recently, Senthilkumaran et al. [27] demonstrated that IA combination of 10 mg morphine and 20 ml of 0.5% bupivacaine reduces requirements for systemic opiate analgesia after arthroscopic ACL reconstruction.

Tramadol induces its peripheral analgesic effects through the activation of opioid receptors and enhances the function of the spinal descending inhibitory pathway by inhibition of reuptake of both 5-hydroxytryptamine (5-HT) and norepinephrine [5, 25]. In this regard, Kapral et al. [18] reported that tramadol increases the duration of analgesia when added to mepivacaine for axillary plexus blockade and concluded that tramadol can act as an adjuvant to local anesthesia. Alagol et al. [2] have suggested 100 mg of intraarticular tramadol as an appropriate analgesic with the least possible side effects. Likar et al. [23] also reported that 1 mg morphine provides better analgesia than 10 mg tramadol injected intraarticularly after arthroscopic knee surgery; however, it has been shown that 10 mg IA tramadol is not effective for pain management after arthroscopic knee surgery [2]. Recently, Zeidan et al. found that a combination of tramadol 100 mg with bupivacaine 0.25% provides a lower VAS pain scores, a longer duration of analgesia and a decrease in the 24 h consumption of rescue analgesia without any side effects after arthroscopic knee surgery, when compared with groups receiving bupivacaine or tramadol injection alone. They noted also earlier recovery of unassisted ambulation and home discharge for the combination group [38]. Moreover, similar results were obtained by Tuncer et al. [33].

In this study, in the MB group the longer analgesic duration, the least quantity of analgesic consumption, considerable reduction in VAS scores after 2, 4 and 24 h, shorter discharge time and ambulation time can be the outcome of the long-term and anti-inflammatory effects of morphine versus tramadol.

One of the most important factors related to the severity of pain after knee surgery is the type of the knee disorders and their surgical trauma. For this reason, all of our patients were admitted with ACL insufficiency and experienced the same surgical trauma (arthroscopic ACL reconstruction). Patients were between 16 and 37 years old that indicated they had not degenerative changes in the knee.

Table 3 Postoperative quality of analgesia and time for ambulation and discharge, presented as mean ± SD

	Group MB ($n = 20$)	Group TB ($n = 20$)	Control group ($n = 20$)	P value
Patients requiring rescue analgesia n (%)	9 (45%)	15 (75%)	20 (100%)	0.000
First analgesic requirement time (analgesic duration) (min)	565 ± 33.1	393 ± 25.6	89.6 ± 8.1	0.000
Analgesic consumption (mg)	4.5 ± 2.1	12.5 ± 8.5	32.5 ± 3.5	0.000
Ambulation time (h)	24.3 ± 5.2	30.0 ± 7.5	40.5 ± 7.1	0.000
Discharge time (h)	30.1 ± 4.2	38.7 ± 7.1	48.2 ± 6.3	0.000

Table 4 Postoperative side effects

	Group MB ($n = 20$)	Group TB ($n = 20$)	Control group ($n = 20$)
Nausea n (%)	2 (10%)	2 (10%)	2 (10%)
Vomiting n (%)	1 (5%)	1 (5%)	1 (5%)
Pruritus n (%)	2 (10%)	0 (0%)	0 (0%)
Respiratory depression n (%)	0 (0%)	0 (0%)	0 (0%)

Lack of VAS assessment of the knee flexion during the first 24 h after the operation, which was the consequence of the orthopedic surgeon's recommendation to the patients in keeping the knee still, is regarded as the limitation of the study. Moreover, in regarding with absorption and systemic effects of the drugs used we suggest the assessment of serum level of the drugs and their comparison at different intervals in further studies.

Of clinical relevance of this study, it can be said that local administration of selected opioids can effectively relieve postoperative pain after arthroscopic ACL reconstruction without serious side effect induction and can also decrease dosage of anodyne consumption like systemic opioids or other medications frequently associated with side effects.

Conclusions

This study indicates that intraarticular combination of 10 mg morphine with bupivacaine 0.5% provides effective pain relief, longer analgesic duration, less analgesic requirement, shorter unassisted ambulation and discharge time without additive side effects than a combination of 100 mg tramadol with bupivacaine 0.5% after ACL reconstruction arthroscopy.

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Conflict of interest None.

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