



Effects of intra-articular levobupivacaine, fentanyl-levobupivacaine and tramadol-levobupivacaine for postoperative pain in arthroscopic knee surgery

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Objective: The aim of this study was to compare the postoperative analgesic efficacy of intra-articularly injected levobupivacaine, levobupivacaine-fentanyl, and levobupivacaine-tramadol combinations.

Methods: Eighty patients scheduled for elective knee arthroscopy were divided randomly into 4 groups of 20 patients each. Group 1 (the control group) received intra-articular saline, Group 2 received levobupivacaine 2.5 mg/ml, Group 3 received levobupivacaine 2.5 mg/ml + tramadol 50 mg, and Group 4 received levobupivacaine 2.5 mg/ml + fentanyl 150 mcg. All patients were operated on under general anesthesia, and a total of 20 ml study solution was injected: 7 ml subcutaneously before surgery and 13 ml intra-articularly upon completion of surgery. For postoperative, pain visual analogue scale (VAS) was assessed at the 1st, 2nd, 4th, 8th, 12th, and 24th hours postoperatively. Patients with a VAS score over 5 received diclofenac sodium, and the need for rescue analgesics was recorded.

Results: At the 1st, 2nd, 4th, 8th, 12th, and 24th postoperative hours, Group 3 and Group 4 had statistically significant lower VAS scores of pain ($p < 0.01$). Postoperative rescue analgesic requirements were different among the groups. The postoperative 1st hour analgesic requirement was statistically significantly lower in Group 3 and Group 4 when compared to the other groups ($p < 0.01$). At the postoperative 2nd and 4th hours, analgesic requirements were statistically significantly lower in Group 3 than in the other groups ($p < 0.01$). Analgesic requirements were statistically significantly lower in Group 3 and Group 4 than in the other groups ($p < 0.01$). Analgesic requirements at the 12th and 24th postoperative hours did not show any statistically significant difference ($p > 0.05$).

Conclusion: The results indicated that levobupivacaine combined with either fentanyl or tramadol decreased rescue analgesic requirements when compared to levobupivacaine alone.

Keywords: Analgesic need; fentanyl; intra-articular; knee surgery; levobupivacaine; postoperative pain; tramadol.

Arthroscopic knee surgeries are commonly performed day case surgeries; pain is encountered as one of the obstacles delaying hospital discharge and preventing early

rehabilitation. Systemic opioid and non-opioid analgesics are used to treat pain resulting from central and peripheral nerve blockades, intra-articular drug admin-

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istration, and knee arthroscopies.^[1] When an efficient analgesia is provided through intra-articular injection, the number of systemic adverse events is reduced.^[2] Studies report higher success rates regarding intra-articular administration of local anesthetics, with bupivacaine being the most commonly preferred local anesthetic.^[3]

Levobupivacaine is the S(-) isomer of bupivacaine. In experimental animals, it has been demonstrated that cardiovascular and central nervous system toxicity due to anesthetics was minimal for levobupivacaine compared to bupivacaine, and it was better tolerated in studies performed on voluntary human participants.^[4]

Intra-articular administration of local anesthetics provides adequate but short-term analgesia.^[5] Therefore, various adjuvant agents are added to local anesthetics.^[6] Opioids are the most commonly used adjuvant agents administered intra-articularly.^[7-10] However, there are few studies related to intra-articular use of tramadol, which is a μ -opioid receptor agonist and a reuptake inhibitor of norepinephrine and serotonin.^[11-13]

The aim of this study was to compare the postoperative analgesic efficiency of intra-articularly injected levobupivacaine when combined with fentanyl and tramadol.

Patients and methods

After approval by the local ethical committee and written informed consent was provided, 80 ASA grade 1-2 patients aged 20-60 years old scheduled for meniscopathic knee surgery in the Orthopedics Clinic were divided randomly into 4 groups. The study was planned to be a prospective randomized double-blind study.

Patients with cardiovascular, pulmonary, hepatic, renal, neuropsychiatric, allergic, endocrine diseases, alcohol or drug addiction, and local anesthetics allergy were excluded from the study. Additionally, individuals >35% above or <20% below than their ideal weight as well as pregnant and nursing women were excluded from the study. Premedication was performed in none of the cases. In the patients of the 3 experimental groups, a venous access was performed with 20-gauge IV catheter in the dorsal side of the hand after standard monitorization in the operating room, and general anesthesia induction was provided by using 1-2 μ g/kg of fentanyl, 5-7 mg/kg of thiopental, and 0.5 mg/kg of atracurium; orotracheal intubation was performed. Anesthesia was maintained with sevoflurane in a mixture with 50% O₂ and 50% N₂O as carrier gases. Groups were labeled randomly as 1 of 4 groups by the sealed opaque envelope method.

Group 1: Control Group

Group 2: Levobupivacaine 2.5 mg/ml

Group 3: Levobupivacaine 2.5 mg/ml+50 mg Tramadol

Group 4: Levobupivacaine 2.5 mg/ml+50 mcg Fentanyl

The selected anesthetics were administered by the surgeon into the skin and subcutaneous layer of the area through the port side in the intra-articular space where the knee arthroscopy would be performed in a volume of 7 ml before and 13 ml after surgery. To standardize the type and duration of the surgical procedure, only patients undergoing arthroscopic meniscectomy were included in our study, and drain was not placed in these patients after the surgical procedure.

Pain score at rest and in motion was assessed by using a 10-cm pain VAS at the 1st, 2nd, 4th, 8th, 12th, and 24th hours pre- and postoperatively. In patients with a score of more than 5 on the VAS scale, 50 mg oral diclofenac sodium was given, and 24-hour analgesia requirement was recorded.

During assessment of the data obtained from the study, NCSS 2007 and PASS 2008 Statistical Software (NCSS, Kaysville, Utah, USA) programs were used for statistical analysis. During assessment of the study data, one-way ANOVA test was used for comparison of qualitative data with normal distribution in addition to descriptive statistical methods (mean, standard deviation). Kruskal-Wallis test was used for the intergroup comparisons of parameters without normal distribution, and Mann-Whitney U test was used for the determination of the group causing difference. Post hoc analyses were performed to determine which group differed to the point of statistical significance. Chi-square test was used for the comparison of qualitative data. The results were evaluated in 95% confidence interval and at a significance level of $p < 0.05$.

Results

Gender, age, weight, and height were not statistically significantly different between the groups ($p > 0.05$) (Table 1).

Preoperative VAS scores showed statistically significant differences ($p < 0.05$) (Table 2). Preoperative VAS scores of Group 1 were statistically significantly higher compared to those of Group 4 ($p = 0.002$, $p < 0.01$).

There is a statistically significant difference of average VAS at the 1st hour between the groups ($p < 0.01$). In the post hoc analyses performed to determine which group differed to the point of statistical significance, the average VAS pain score of Group 1 at the 1st hour is statistically significantly less than the average VAS pain score of

Table 1. Demographical data.

	Group 1 (n=20)	Group 2 (n=20)	Group 3 (n=20)	Group 4 (n=20)	p
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
Age	30.15±6.84	32.60±7.02	36.20±8.75	34.70±10.20	0.122
Height	168.0±9.84	174.5±8.66	171.8±9.17	171.8±9.57	0.186
Weight	74.8±12.95	75.8±7.62	79.1±9.90	75.6±10.24	0.563
Gender (female/male)	6/14	5/15	6/14	6/14	0.058

Table 2. VAS score evaluation between groups.

VAS Score at movement	Group 1 (n=20)	Group 2 (n=20)	Group 3 (n=20)	Group 4 (n=20)	*p
	Mean±SD (Median)	Mean±SD (Median)	Mean±SD (Median)	Mean±SD (Median)	
Preop	1.05±1.35 (1.0)	0.75±0.55 (1.0)	0.45±0.60 (0.0)	1.57±1.95 (1.0)	0.021*
1 st hour	3.95±1.76 (4.0)	5.25±1.65 (5.0)	1.70±1.45 (2.0)	2.42±0.96 (2.0)	0.001**
2 nd hour	5.75±1.68 (6.0)	5.00±1.71 (5.0)	1.40±1.23 (1.50)	3.10±1.28 (3.0)	0.001**
4 th hour	4.30±1.34 (4.0)	5.20±1.57 (5.0)	2.55±1.27 (3.0)	5.00±2.05 (5.0)	0.001**
8 th hour	5.2±1.55 (5.50)	5.55±0.94 (6.0)	3.80±2.14 (4.0)	4.10±2.35 (3.0)	0.001**
12 th hour	4.40±1.46 (4.0)	4.20±1.00 (4.0)	2.70±1.86 (3.0)	2.21±1.51 (2.0)	0.001**
24 th hour	3.90±1.58 (4.0)	3.55±0.75 (4.0)	2.20±1.54 (2.0)	2.05±1.47 (2.0)	0.001**

*Kruskal-Wallis test; *p<0.05; **p<0.01.

Group 2 ($p=0.010$, $p<0.05$) and statistically significantly higher than the average VAS pain score of Group 3 and Group 4 ($p=0.001$, $p=0.001$, $p<0.01$). The average VAS pain score of Group 2 at the 1st hour is statistically significantly higher than the average VAS pain score of Group 3 and Group 4 ($p=0.001$, $p=0.001$, $p<0.01$). There is no statistically significant difference between Group 3 and Group 4 regarding VAS measurements at the 1st hour ($p>0.05$).

There is a statistically significant difference between the average VAS pain scores at the 2nd hour between the groups ($p<0.01$). In the post hoc analyses performed to determine which group differed to the point of statistical significance, while there is no significant difference between Group 1 and Group 2 regarding VAS measurements at the 1st hour ($p>0.05$), the average VAS pain score of Group 2 at the 2nd hour is statistically significantly higher than the average VAS pain score of Group 3 and Group 4 ($p=0.001$, $p=0.001$, $p<0.01$). The average VAS pain score of Group 2 at the 2nd hour is statistically significantly higher than the average VAS pain score of Group 3 and Group 4 ($p=0.001$, $p=0.001$, $p<0.01$). Additionally, the average VAS pain score of Group 4 at the 2nd hour was determined to be statistically significantly higher than the average VAS pain score of Group 3 ($p=0.001$, $p<0.01$).

There is a high statistically significant difference be-

tween the average VAS pain scores at the 4th hour between the groups ($p<0.01$). In the post hoc analyses performed to determine which group differed to the point of statistical significance, the average VAS pain score of Group 1 at the 4th hour is statistically significantly higher than the average VAS pain score of Group 2 ($p=0.024$, $p<0.05$) and statistically significantly higher than the average VAS pain score of Group 3 ($p=0.001$, $p<0.01$). The average VAS pain score of Group 2 at the 4th hour is statistically significantly higher than the average VAS pain score of Group 3 ($p=0.001$, $p<0.01$); the average VAS pain score of Group 4 at the 4th hour is statistically significantly higher than the average VAS pain score of Group 3 ($p=0.001$, $p<0.01$).

There is a high statistically significant difference between the average VAS pain scores at the 8th hour according to the groups ($p<0.01$). In the post hoc analyses performed to determine which group differed to the point of statistical significance, the average VAS pain score of Group 1 and Group 2 at the 8th hour is statistically significantly higher than the average VAS pain score of Group 3 and Group 4 ($p=0.026$, $p=0.045$, $p<0.05$). The average VAS pain score of Group 2 at the 8th hour is statistically significantly higher than the average VAS pain score of Group 3 and Group 4 ($p=0.002$, $p<0.01$, $p<0.05$). No statistically significantly different VAS Score is seen between VAS measurements of the

other groups at the 8th hour ($p>0.05$) Figure 1.

There is a high statistically significant difference between the average VAS pain scores at the 12th hour between the groups ($p<0.01$). In the post hoc analyses performed to determine which group differed to the point of statistical significance, the average VAS pain score of Group 1 and Group 2 at the 12th hour is statistically significantly higher than the average VAS pain score of Group 3 and Group 4 ($p=0.007$, $p=0.001$; $p<0.01$). No statistically significantly different VAS Score is seen between VAS measurements of the other groups at the 12th hour ($p>0.05$).

There is a high statistically significant difference between the average VAS pain scores at the 24th hour between the groups ($p<0.01$). In the post hoc analyses performed to determine which group differed to the point of statistical significance, the average VAS pain score of Group 1 and Group 2 at the 24th hour is statistically significantly higher than the average VAS pain score of Group 3 and Group 4 ($p=0.002$, $p=0.001$, $p<0.01$). No statistically significantly different VAS Score is seen between VAS measurements of the other groups at the 24th hour ($p>0.05$) Figure 2.

Analgesic requirements in each group were summa-

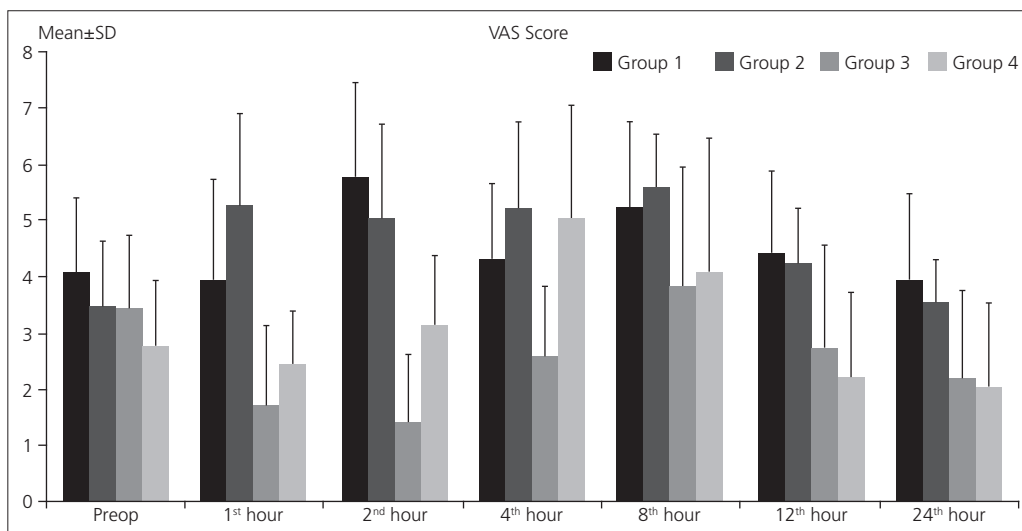


Fig. 1. VAS Scores regarding groups.

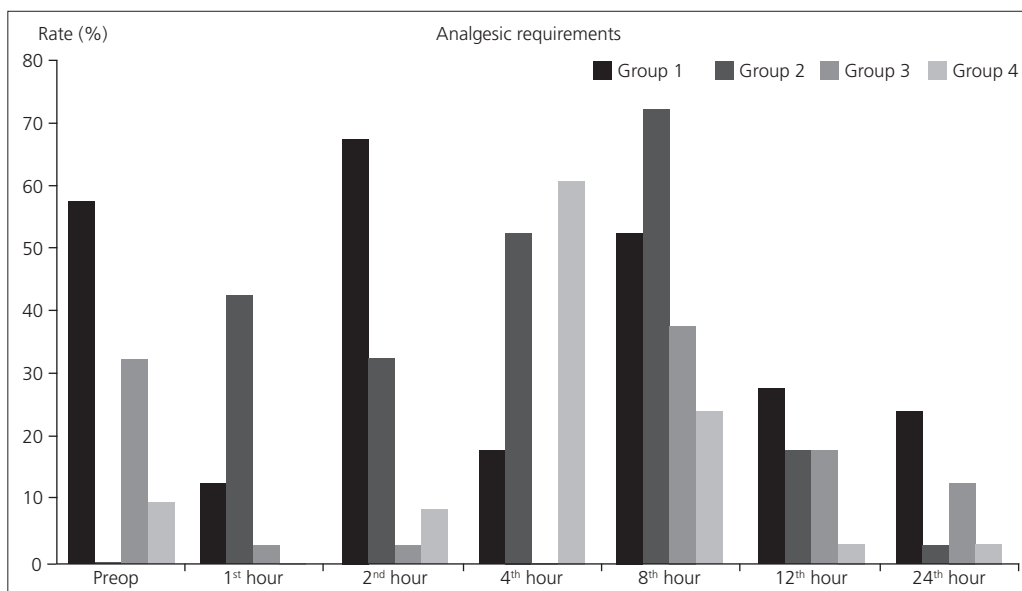


Fig. 2. Analgesic requirements.

rized in Table 3, where analgesic requirement in Groups 3 and 4 was higher compared to Groups 1 and 2 but did not exceed 2 times of analgesic requirements.

Discussion

Arthroscopic knee surgery is among the most commonly performed day case surgical procedures. Success of day case surgical procedures depends on efficient postoperative pain control and early mobilization.^[1] Many postoperative analgesia methods are used in arthroscopy. Systemically-administered analgesic agents, neuraxial blockades, local anesthetic infiltration, and intra-articular injections are the leading methods.^[14]

In the study performed by Ozok et al.^[15] comparing intra-articular and epidural injections of morphine and bupivacaine in arthroscopies for postoperative analgesia, the authors found postoperative pain scores to be less in the groups administered intra-articular injections of the agents. Raj et al.^[16] showed that intra-articular injection of morphine was more effective in postoperative pain control compared to intramuscular injection of the same dose of morphine. In their study, Alagol et al.^[17] administered tramadol through intra-articular and intravenous routes in the same doses. The authors stated that duration of analgesia was longer and incidence of systemic adverse events was lower in intra-articular administration of the agents. In conjunction with these studies indicating the advantages of local administrations and efficacy of intra-articular administrations, we elected intra-articular administrations of the agents for postoperative analgesia in our study.

Local anesthetics are commonly used for intra-articular analgesia. Bupivacaine is the most commonly used local anesthetic for this purpose.^[3]

Clinical studies established that the anesthetic and/or analgesic effects of levobupivacaine were largely similar to the anesthetic and/or analgesic effects of bupivacaine at the same dose.^[18,19] In animal studies, it was shown that cardiovascular and neurological toxicities of levobupivacaine were lower than those of bupivacaine.^[20]

In a study performed in our clinic, we compared intra-articularly administered 2.5 mg/ml and 5 mg/ml levobupivacaine and 5 mg/ml bupivacaine in arthroscopic knee surgery regarding their effects on postoperative pain and analgesic consumption. We observed that intra-articularly administered 5 mg/ml levobupivacaine and 5 mg/ml bupivacaine in arthroscopic knee surgery had similar effects on postoperative analgesia and reduced postoperative analgesic requirement.^[21]

In the study performed by Jacopson et al.,^[22] it was determined that postoperative analgesic requirement cases having intra-articularly administered 5 mg/ml levobupivacaine was less than that of cases having intra-articularly administered 5 mg/ml bupivacaine in day case arthroscopic knee surgeries. These studies can explain the higher 1st hour VAS scores of the levobupivacaine group than the control group in our study. In our study, levobupivacaine was used at concentrations of 0.25%.

Intra-articular administration of local anesthetics provides adequate but short-term analgesia lasting for 4 hours.^[5] Therefore, various adjuvant agents are added to the local anesthetics.^[6] Opioids are the most commonly used adjuvant agents administered intra-articularly.^[7-10] Establishment of the presence of peripheral opioid receptors such as μ and delta and kappa receptors on the peripheral nerve endings further make the use of intra-articularly administered morphine and fentanyl a current issue.^[23]

In the study performed in 20 patients by Mark Tverskoy et al.,^[7] the authors established that efficient analgesia was not provided only in the patients administered lidocaine but also in the patients administered fentanyl and lidocaine. In the study performed by Jawish et al.,^[8] it was determined that the addition of 50 μ g of fentanyl to bupivacaine prolonged the period of analgesic effect to 9 hours. In the study performed by Mandal et al.,^[9] the authors compared the doses of fentanyl administered intra-articularly in day case arthroscopies. They concluded that a 50 mcg dose of fentanyl was optimal. In agreement with this finding, we chose to add 50 μ g of fentanyl to

Table 3. 24-hour period analgesic requirements.

Analgesic requirement	Group 1 (n=20)		Group 2 (n=20)		Group 3 (n=20)		Group 4 (n=20)		Total
	n	%	n	%	n	%	n	%	
Analgesic requirement (-)	0	0	1	5	3	15	1	5.3	5
1 time	1	5	2	10	10	50	13	68.4	26
2 times	8	40	7	35	7	35	5	26.3	27
3 times	7	35	9	45	0	0	0	0	16
4 times	4	20	1	5	0	0	0	0	5

levobupivacaine in Group 4 of our study.

In the study performed by Varkel V. et al.^[10] comparing 3 mg of morphine and 50 µg of fentanyl administered intra-articularly with a control group, while they found pain scores of all groups at all hours to be lower than those of the control group, pain scores of the fentanyl group were determined to be lower than those of the morphine group at all hours except the 1st hour.

Tramadol exerts its analgesic effect by affecting opioid receptors, increasing the function of spinal inhibitory pathways, and inhibiting reuptake of both 5 hydroxytryptamine and norepinephrine. Causing less sedation, less respiratory depression, and having lower abuse potential compared to opioids has increased its use in recent years. However, there are insufficient studies at this time on intra-articular use of tramadol.^[11–13]

Bezadeoglu et al.^[11] compared periarticular incisional injection of 100 mg tramadol and 10 ml bupivacaine 0.5% and periarticular incisional injection of 20 ml bupivacaine 0.25% and 10 ml of bupivacaine 0.5% after arthroscopic meniscopathic surgery with respect to VAS scores at rest and during active flexion and postoperative analgesic consumptions. The authors found VAS scores at rest and during active flexion and postoperative 24-hour analgesic consumption to be lower in the group administered tramadol.

In the study performed by Zeidan et al.^[12] comparing intra-articular injection of bupivacaine 0.25%, 100 mg tramadol, and bupivacaine-tramadol combination, it was reported that there were lower VAS scores and lower postoperative 24-hour analgesic consumptions in the bupivacaine-tramadol combination group.

However, in the study performed by Hosseini H et al.^[13] comparing intra-articular injection of 10 mg of morphine and bupivacaine 0.5% combination and 100 mg tramadol and bupivacaine 0.5% combination in arthroscopic anterior cruciate ligament reconstruction, it was determined that there were lower VAS scores, lower analgesic consumptions and earlier mobilization in the morphine-bupivacaine group.

To standardize the type and duration of the surgical procedure, only the patients undergoing arthroscopic meniscectomy were included in our study. A difference was determined in the operation periods of the studies including patients undergoing arthroscopic knee surgery with different methods and discharged at postoperative Hour 24, and a correlation was observed between operation period and postoperative pain severity.^[24]

In our study, VAS scores of Group 1 at the 1st hour are lower than those of Group 2 and higher than those

of Groups 3 and 4. VAS scores of Groups 1 and 2 are higher than those of Groups 3 and 4 at the 2nd, 4th, 8th, 12th, and 24th hours. VAS scores of Group 4 were found to be higher than those of Group 3 at the 2nd and 4th hours. A difference was determined between VAS scores of Groups 3 and 4 at the other hours. Taking into consideration neglected analgesic use in the 24-hour postoperative period, higher values in average VAS pain scores of Group 1 indicate that analgesic effect should be supported by local mechanisms to provide sufficient analgesia in the postoperative period in our study.

While there was no case that did not require analgesia in the control group, oral analgesic consumption occurred 54 times in total. Oral analgesic consumption occurred 47 times in total in 19 of 20 cases where 2.5 mg/ml of levobupivacaine was administered intra-articularly.

Analgesic consumption in both groups administered tramadol+bupivacaine and fentanyl+bupivacaine was 23 and equal.

In conclusion, levobupivacaine 0.25% applied for day case surgery as arthroscopic knee surgery combined with either fentanyl or tramadol decreased rescue analgesic requirements and provided efficient analgesia compared to levobupivacaine alone.

Conflicts of Interest: No conflicts declared.

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