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ORIGINAL ARTICLE

Intraarticular levobupivacaine or bupivacaine administration decreases pain scores and provides a better recovery after total knee arthroplasty

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Abstract
Purpose The aim of this prospective randomized blinded controlled study was to compare the efficacy of the two local anesthetics, intraarticular bupivacaine and levobupivacaine administration, versus control for postoperative pain control and functional recovery. Length of hospital stay, opioid consumption, and the side effects of opioids were also evaluated.
Methods Sixty patients of American Society of Anesthesiologists class I–III undergoing elective knee arthroplasty under spinal anesthesia were randomized into three groups. Groups B ($n = 20$) and L ($n = 20$) both received 150 ml solution intraarticularly, containing 200 mg bupivacaine or 200 mg levobupivacaine combined with 0.5 mg epinephrine, respectively, at the end of the surgery. Group C ($n = 20$) received 150 ml saline intraarticularly. Postoperatively, all groups received injections through the intraarticular catheters in quantities of 120 mg (levobupivacaine for group L, bupivacaine for group B) and 0.5 mg epinephrine whereas group C received a saline bolus at 10 and 22 h. Patients were given tramadol by intravenous patient-controlled analgesia (PCA), and sodium diclofenac 75 mg intramuscularly was used for rescue analgesic medication. Visual analogue score (VAS) for pain at rest and during mobilization (which was defined as flexion exercise supported by physiotherapist in postoperative first 8 h and afterward a 3-m walk with walker), consumption of tramadol, side effects, and patient satisfaction were recorded until the 48th hour postoperatively.
Results Area under the curve values for VAS were lower in groups B and L compared to the control, both at rest and during mobilization (first 48 h) ($P = 0.032$ and $P = 0.029$, respectively). Tramadol consumption was lower ($P < 0.05$), patient satisfaction as evaluated with a five-point Likert score (completely comfortable; quite comfortable; slight discomfort; painful; very painful) was higher ($P = 0.03$), and length of hospital stay was shorter ($P = 0.03$) in groups B and L compared to group C.
Conclusion Intraarticular bupivacaine and levobupivacaine provided better postoperative analgesia both at rest and during mobilization in total knee replacement surgery compared to control. Tramadol consumption and hospital stay were also decreased in the study groups.

Keywords Intraarticular · Levobupivacaine · Bupivacaine · Total knee arthroplasty

This article is dedicated to Yesim Ates who passed away on May 26, 2010.

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Introduction

Total knee arthroplasty (TKA) is a common and major orthopedic procedure. It has been reported that half the patients undergoing TKA experience severe pain in the early postoperative period [1]. Postoperative analgesia for TKA is often multimodal and may include several analgesic techniques, such as intravenous opioids, peripheral nerve blocks, epidural analgesia, intraarticular or intrasynovial opioids/local anesthetics, and oral analgesics [2].

Epidural analgesia is of proven benefit but may be associated with side effects such as urinary retention, hypotension, and epidural hematoma [3, 4].

Intraarticular analgesia is an improving modality. However, there are a limited number of studies investigating intraarticular infusion of bupivacaine for total knee arthroplasty with conflicting results [5–7].

To our knowledge, no prior study has used intraarticular levobupivacaine, a less toxic agent, or compared it with bupivacaine and saline. The aim of this prospective randomized blinded controlled study was to compare the efficacy of intraarticular bupivacaine and levobupivacaine administration versus control for postoperative pain management at rest and during mobilization. Length of hospital stay, postoperative tramadol consumption, patient satisfaction, and postoperative nausea–vomiting (PONV) were also evaluated.

Methods

Sixty patients of American Society of Anesthesiologists (ASA) class I–III, 18–75 years of age, were enrolled in this prospective, randomized blinded study after written informed consent was obtained. The study was approved by the hospital Ethics Committee. All patients were scheduled to undergo elective unilateral tricompartment knee arthroplasty at the Department of Orthopedic Surgery in Medical Faculty Hospitals of Ufuk University and Ankara University between June 2008 and April 2009. Exclusion criteria were contraindication to spinal anesthesia, severe systemic disease, known allergy or intolerance to study drugs, simultaneous bilateral TKA, neuromuscular deficit, sensory disorder in the leg to be operated, inability to comprehend pain scales, or refusal of the patient.

Patients were randomized into three groups using a sealed envelope technique before spinal anesthesia. The authors collecting postoperative data (K.D. and A.S.) were blinded to the study groups. Group B ($n = 20$) received intraoperative intraarticular bupivacaine followed by bolus injections, group L ($n = 20$) received intraoperative intraarticular levobupivacaine followed by bolus injections, and group C ($n = 20$), which was the control group, received saline intraarticularly.

Patients were premedicated with midazolam 2 mg and atropine 0.5 mg intravenously. Standard monitoring techniques were used, including electrocardiography (ECG), noninvasive blood pressure (NIBP), and pulse oximetry. All operations were performed by one of the three surgeons under spinal anesthesia with 3 ml hyperbaric bupivacaine (5 mg/ml) at the L3–L4 or L4–L5 interspace using tourniquet control, a medial peripatellar approach, and patellar resurfacing.

Groups B ($n = 20$) and L ($n = 20$) both received 150 ml solution intraarticularly, containing 200 mg bupivacaine or 200 mg levobupivacaine, respectively, combined with 0.5 mg epinephrine, at the end of the surgery. Group C ($n = 20$) received 150 m saline intraarticularly. The solution was given in 3×50 ml syringes. The first 100 ml was used after cementing of the modular prosthesis and before replacing the polyethylene insert. First, 50 ml of 100 ml was injected into the posterior part of the capsule and the intercondylar area; second, 50 ml of 100 ml was infiltrated into the anterior part of the capsule, the collateral ligaments, and along the femur and tibia. Group C (intraarticular saline infiltration group) received 100 ml saline intraarticularly to the same anatomic locations.

At the end of surgery, a postsurgical (negative pressure drainage) drain was placed lateral to the incision, draining the anterior part of the joint. A second 20-gauge catheter was placed entering the joint about 5 cm proximal to the surgical drain, and the end of the catheter was placed in the lateral gutter of the joint. The remaining 50 ml of solution was infiltrated into the subcutaneous tissue after closure of the capsule. All patients were given another 50 ml solution in 2×25 ml syringes from the intraarticular catheter postoperatively. The first 25 ml administration was at 10 h and second was at 22 h after the operation; these administrations were given 30 min before the physical therapy sessions. At each interval, group B or group L received 120 mg (24 ml) local anesthetic (bupivacaine for group B, levobupivacaine for group L, respectively) and 0.5 mg (1 ml) epinephrine whereas group C received a saline bolus. Boluses were administrated after clamping the drain, which was declamped after 30 min. The intraarticular catheter was removed after the second bolus.

All patients received patient-controlled analgesia (PCA) with tramadol after the operation as 50-mg boluses with 15-min lockout period, 4-h limit of 200 mg, for 48 h. Diclofenac 75 mg was used as a rescue analgesic that could be repeated every 6 h if the visual analogue scale (VAS) for pain was 50 or more with a maximum daily dose of 300 mg. In case of PONV, metoclopropamide was administered intravenously.

Postoperative data were collected by two of the authors blinded to the study groups. All patients were monitored for pain intensity by using a 100-mm VAS (0 = no pain, 100 = worst pain imaginable) for pain at rest and during mobilization (which was defined as flexion exercise supported by a physiotherapist in the first 8 h postoperative and afterward a 3-m walk with a walker). Patient satisfaction was evaluated with a five-point Likert score [8] (completely comfortable; quite comfortable; slight discomfort; painful; very painful). Hemodynamic parameters [mean arterial blood pressure (MAP), heart rate (HR)] and adverse effects such as PONV were also noted. Data on the number of

Table 1 Comparison of demographic data (mean ± SD), duration of surgery (mean ± SD), first analgesic time (mean ± SD), ambulation ratio at first 24 h, and length of stay (median and range) among the study groups

Parameter	Group B, bupivacaine ($n = 20$)	Group L, levobupivacaine ($n = 20$)	Group C, control ($n = 20$)	*P*
Gender (F/M)	15/5	16/4	18/2	0.437
Age (years)	67 ± 7	71 ± 11	71 ± 6	0.613
ASA (I–II/III)	15/5	16/4	14/6	0.765
Weight (kg)	74 ± 15	75 ± 14	77 ± 16	0.523
Height (cm)	166 ± 26	162 ± 24	163 ± 25	0.367
Duration of surgery (min)	102 ± 20	85 ± 29	90 ± 23	0.266
First analgesic time (h)	5.0 ± 1.2	5.2 ± 1.7	2.1 ± 0.6[a]	0.0001
Ambulation without help (in first 24 h) (+/–)	12/8	14/6	6/14[a]	0.031
Length of stay (days)	2.5 (1.8–3)	2.3 (2–2.9)	4.5 (3.9–4.9)[a]	0.033

[a] Group B and group L versus group C

demands and boluses of PCA were collected at the 1st, 2nd, 4th, 8th, 12th, 24th, and 48th h postoperatively.

Time of first analgesic use and 48-h total tramadol and sodium diclofenac consumption were recorded. Infiltration mixtures were prepared by two of the authors (Z.K., H.S.). Postoperative infiltrations were applied by a senior trainee of anesthesiology. Patients were discharged after ambulation without help, and removal of drains, with no wound or fever, were achieved.

Sample size calculation was based on an expected difference of 20 mm in the VAS measurement of pain between group means, based on a reported value of minimal clinically important differences in acute pain, on a standard deviation of 32, obtained from previous studies, with $P = 0.90$ and $\alpha = 0.05$. A sample size of 18 patients per group was obtained. All statistical calculations were performed using SPSS version 11.5 (Statistical Packages for the Social Sciences). Numerical variables were analyzed by using the Kolmogrov–Smirnov test. The data were presented as mean ± SD or median (min–max). The categorical data (ASA, gender, rescue analgesic, mobilization, PONV, and patient satisfaction) were analyzed with the chi-square test. For normally distributed variables, differences between the groups were determined by one-way analysis of variance (ANOVA) followed by the Tukey test. Kruskal–Wallis test followed by Dunn test was used for variables not normally distributed (length of stay). A *P* value <0.05 was considered statistically significant.

Results

Data for gender, ASA, and ambulation are expressed as a ratio; age, weight, height, duration of surgery, and first analgesic time as mean ± SD; and length of stay as median and range. There were no statistically significant differences among the three groups (Table 1). HR and MAP in the three groups were similar during and after the surgery.

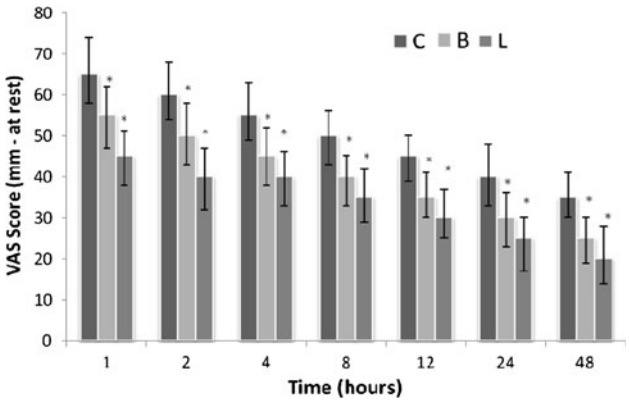

Fig. 1 Postoperative visual analogue score (VAS) scores at rest among study groups (mean ± SD). *C*, group C (control group); *B*, group B, received intraoperative intraarticular bupivacaine; *L*, group L, received intraoperative intraarticular levobupivacaine. $P < 0.05$, groups B and L versus group C

In the postoperative period, VAS scores at the 1st, 2nd, 4th, 8th, 12th, 24th, and 48th h at rest and during mobilization were significantly lower in group L and group B compared with group C ($P = 0.03$ and $P = 0.03$, respectively) (Figs. 1, 2). In the postoperative period, area under curve (AUC) values of VAS scores of group L and group B were significantly lower than AUC values of group C ($P < 0.05$). In total consumption of tramadol, AUC values for group L and group B were significantly less than AUC values of group C ($P < 0.01$) (Fig. 3). Time to first request for analgesic was 5.0 ± 1.2 h in group B, 5.2 ± 1.7 h in group L, and 2.1 ± 0.6 h in group C ($P < 0.01$) (see Table 1).

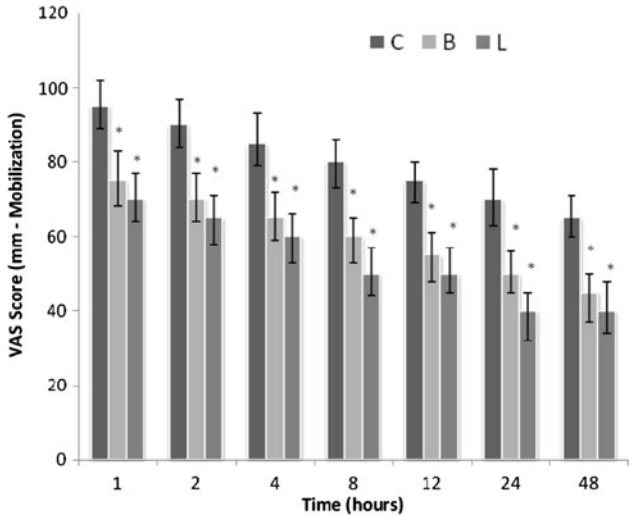

Fig. 2 Postoperative VAS scores during mobilization among the study groups (mean ± SD). *C*, group C (control group); *B*, group B, received intraoperative intraarticular bupivacaine; *L*, group L, received intraoperative intraarticular levobupivacaine. *$P < 0.05$, groups B and L versus group C

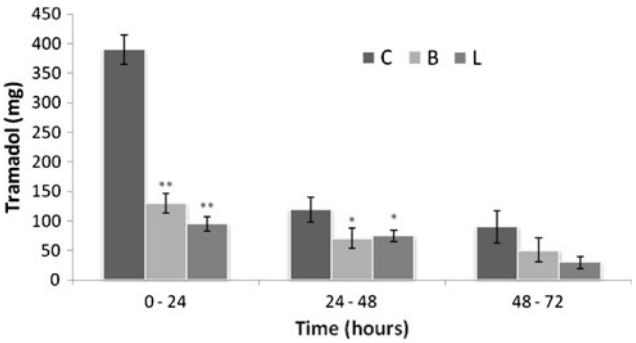

Fig. 3 Area under curve (AUC) values for total tramadol consumption among the study groups. *C*, group C (control group); *B*, group B, received intraoperative intraarticular bupivacaine; *L*, group L, received intraoperative intraarticular levobupivacaine. *$P < 0.05$, groups B and L versus group C

During their hospital stay, 6 patients from group B, 5 patients from group L, and 9 patients from group C of 20 patients from each group needed sodium diclofenac for rescue medication ($P = 0.38$). The numbers of patients who were able to ambulate without help in the first 24 h postoperatively in groups B and L were significantly higher than in group C (see Table 1).

No significant differences were seen for the number of patients who experienced PONV between groups B, L, and C ($P = 0.22$). In addition, no other complications or side effects or signs of infection were seen in any of the groups.

Length of hospital stay was significantly shorter in group L and group B than in group C ($P < 0.05$).

Table 2 Evaluation of postoperative patient satisfaction according to Likert score among the study groups

Score	Group B, bupivacaine ($n = 20$)	Group L, levobupivacaine ($n = 20$)	Group C, control ($n = 20$)	*P*
Completely comfortable	8	9	2	0.037[a]
Quite comfortable	6	6	3	
Slight discomfort	3	3	5	
Painful	2	2	6	
Very painful	1	0	4	

Data represent number of patients (8)

[a] Groups B and L versus group C

Furthermore, patient satisfaction was higher in both group L and group B compared to the control group, C ($P < 0.05$) (Table 2).

Discussion

In this study, two local anesthetics, bupivacaine and levobupivacaine administered intraarticularly, were compared with intraarticular saline for postoperative pain control following TKA. The primary endpoint of this study was to compare the efficacy of bupivacaine and levobupivacaine administration for postoperative pain control by VAS during mobilization. Furthermore, secondary endpoints were to decrease the time of first ambulation without help, tramadol and postoperative analgesic consumption (48 h), length of hospital stay, and overall patient satisfaction.

Postoperative pain after TKA can be difficult to manage and may delay recovery. Although many analgesia protocols have been evaluated, none is optimal. Nevertheless, analgesia with the use of parenteral opioids, femoral block, or epidural analgesia can be associated with some side effects [9]. Epidural analgesia is of proven benefit and has been demonstrated to be more effective than PCA alone; however it is associated with side effects such as spinal headache, neurogenic bladder, hypotension, respiratory depression, cardiac decompensation, hematoma, risk of infection, and abscess [10–12]. Other possible pain modalities include single, multiple, or continuous nerve blocks. They reduce the side effects related to epidural and PCA, but for effective pain relief it may be necessary to block the sciatic, femoral, and obturator nerves [13, 14]. Therefore, a good and easy analgesia technique that is obtained by locally injected drugs around a total knee prothesis may reduce pain and consumption of opioids, facilitate mobilization, improve patient satisfaction, and also decrease hospital stay [15, 16]. In this study, for the first time the widely used local anesthetics bupivacaine and

levobupivacaine were compared in a relatively new intra-articular analgesic technique, and this approach was shown to be associated with beneficial outcomes.

Levobupivacaine is the *S*-enantiomer of bupivacaine and has a longer duration of action [17]. When compared to bupivacaine, levobupivacaine appears to have a larger margin of safety in terms of cardiovascular and central adverse effects when used in large doses [18–20]. In this study, high doses of both bupivacaine and levobupivacaine were used when compared to epidurally administered doses of both agents [10]; however, no side effects were encountered from intraarticular administration of these two agents. This finding may show that intraarticular administration of these potentially toxic agents may be considered relatively safe.

The results of pain scores were evaluated by VAS and AUC values, which were calculated to represent a global evaluation of data. These results have shown that both levobupivacaine and bupivacaine are comparatively effective in reducing AUC values for VAS both at rest and during mobilization. In the local anesthetic groups, the difference of postoperative VAS at 1 h compared to the control group, which is 30% lower, can be attributed to the effect of the intraarticular local anesthetic administered at the end of surgery. However, adjuvants can be added to increase the efficacy. VAS pain scores can arguably be an invalid reflection of analgesia in the setting of PCA therapy. However, as it is the most widely used scoring system, VAS therefore was used for evaluating pain scores in this study.

Intraarticular injection of bupivacaine and epinephrine with or without adjuncts has previously been shown to decrease the need for opioids after TKA [15, 21]. Continuous bupivacaine infusion has also been shown to relieve pain after shoulder surgery [22]. In this study, postoperative tramadol consumption by PCA and rescue analgesic use were both lower in the study groups compared to control. AUC values for tramadol consumption also showed a significant reduction in both intraarticular drug administration groups ($P < 0.01$).

Allen et al. [23] have shown that intraarticular injections following TKA reduce requirements for postoperative analgesics and allow earlier discharge from the hospital. Busch et al. [24] used periarticular ropivacaine, ketorolac, epimorphine, and epinephrine for postoperative analgesia in their study. They found that multimodal drugs can significantly reduce the requirements for PCA and improve patient satisfaction. In a similar study, Vendittoli et al. [16] concluded that periarticular injection of large doses of local anesthetics significantly decreased opioid consumption.

In this study, side effects of opioids and length of hospital stay were also evaluated. There was no significant difference in the incidence of PONV in all groups. In group L and group B, length of stay was shorter and patient satisfaction was higher.

There are some studies concerning intraarticular bupivacaine or ropivacaine for relieving the postoperative pain of arthroplasty of the knees [21, 25]. This study is, therefore, the first to show that intraarticular levobupivacaine is as effective as bupivacaine in pain relief to reduce postoperative VAS scores, to improve patient satisfaction, and to reduce hospital stay.

Besides several analgesic techniques, intraarticular analgesia is an improving modality for commonly applied major orthopedic procedures such as TKA. However, there are a limited number of studies investigating intraarticular infusion of bupivacaine, and to the authors' knowledge there has been no controlled study comparing intraarticular levobupivacaine administration to bupivacaine. As the other methods, the intraarticular injection technique also has some disadvantages and side effects. One of these is a risk for uncontrolled extraarticular leak. In our study, the study solutions were injected into the posterior (intercondylar area) and anterior part of the capsule, along the collateral ligaments, femur, and tibia. The end of the catheter was placed in the lateral gutter of the joint. However, the amount of the leak, if present, may be determined only by experimental studies. Another one is intraarticular catheter infection, which can be decreased by placement of sterile catheters [25, 26]. It has been shown that local anesthetics not only serve as agents for pain control but possess antimicrobial activity as well [27]. None of the patients in this study experienced any type of infection or complained of being uncomfortable. These disadvantages may be our study's limitations as well. First, there may be a risk of extraarticular leak, which cannot be demonstrated, and second, the number of the study groups may be too small to evaluate any catheter infection. On the other hand, an adjuvant could be added to the intraarticular local anesthetics, or the infusion method could be used instead of boluses for future studies.

Clinical implications of this study are that intraarticular local anesthetic levobupivacaine or bupivacaine administration can be a good alternative to epidural analgesia or IV-PCA for postoperative pain control in TKA.

Conclusion

The results of this study validate the idea that intraarticular application of bupivacaine or levobupivacaine, compared to control, by infiltration and bolus injections may provide better analgesia at rest and during mobilization, improve patient satisfaction, decrease opioid consumption, hasten postoperative ambulation, and decrease length of stay following TKA surgery. To our knowledge this is the first

study to examine the effectiveness of levobupivacaine administered intraarticularly for TKA patients.

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