A comparison of analgesic effect of intra-articular levobupivacaine with bupivacaine following knee arthroscopy

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ABSTRACT

الأهداف: مقارنة آثار التسكين بعد العملية لعقار ليفوبوبيفاسين داخل المفصل مع عقار بوبيفاسين عقب إجراء تنظير مفصل الركبة.

الطريقة: أجريت دراسة مزدوجة مجهولة الطرفين شملت 40 مريضاً تراوحت أعمارهم بين 20–60 عاماً، خضعوا لتنظير مفصل الركبة الاختياري، حيث تم إدراجهم في هذه الدراسة التي أجريت بمستشفى تيبيسيك التعليمي ومركز الأبحاث – أزمير – تركيا، خلال الفترة ما بين يناير2007م وحتى يونيو 2007م. كان بروتوكول التخدير العام نفسه على كل المرضى. تم تقسيم المرضى عشوائياً إلى مجموعتين عند نهاية الجراحة (عدد=20). المجموعة (L) تلقت 20ml 0.5% من عقار ليفوبوبيفاسين وتلقت المجموعة (B) مقدار 20ml 0.5% من عقار بوبيفاسين داخل المفصل. قمنا بتقييم مستوى الألم بعد العملية الجراحية (بواسطة نقاط انالوق المرئية عند الساعات الأولى، الثانية، الرابعة، السادسة، الثانية عشرة والأربعة والعشرون بعد العملية) والوقت المطلوب للتخدير الأولي (الفترة المقاسة من نهاية الجراحة حتى الحاجة إلى المزيد من التخدير) والكمية الكاملة لاستهلاك التخدير خلال 24 ساعة.

النتائج: لم يكن هنالك فرقاً ملحوظاً في نقاط الألم بعد العملية للمرضى بين المجموعتين. لم تكن لدى أوقات متطلبات التخدير الأولي فرقاً إحصائياً. لم يحتاج 12 مريضاً في المجموعة (L) الـ(60%) و9 مرضى في المجموعة (B) بـ(45%) إلى التخدير الإضافي خلال 24 ساعة (p>0.05). لم يتبين وجود مضاعفات أو أثار جانبية ذات صلة إلى المعالجة داخل المفصل.

خاتمة: تظهر نتيجة الدراسة أن مقدار 20ml 0.5% من عقار ليفوبوبيفاسين توفر التخدير الفعال وذلك متشابه مع المقدار المقدم من عقار بوبيفاسين والبالغ 20ml 0.5%.

Objectives: To compare the postoperative analgesic effects of intra-articular levobupivacaine with bupivacaine following knee arthroscopy.

Methods: Forty patients, aged between 20-60 years and undergoing elective knee arthroscopy were enrolled into the study protocol that was carried out in Tepecik Education and Research Hospital, Izmir, Turkey between January and June 2007. General anesthesia protocol was the same in all patients. At the end of surgery, the patients were randomly assigned into 2 groups (n=20 in each group). Group L received 20 ml 0.5% levobupivacaine and Group B received 20 ml 0.5% bupivacaine intra-articularly. We evaluated the level of postoperative pain (by visual analoque scale at 1, 2, 4, 6, 12, and 24 hours after surgery), first analgesic requirement time (period measured from the end of the surgery until further analgesia was demanded), and total analgesic consumption during 24 hours.

Results: There were no significant difference in the postoperative pain scores of the patients between groups. The first analgesic requirement times were not statistically different. Twelve patients in Group L (60%) and 9 patients in Group B (45%) needed no additional analgesic during the 24 hours (p>0.05). No complications and side effects were found related to the intra-articular treatment.

Conclusions: The results of the study show that intra-articular 20 ml 0.5% levobupivacaine provides effective analgesia comparable to that provided by 20 ml 0.5% bupivacaine.

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Peripheral use of local anesthetics for the treatment of postoperative pain has gained increased attention and found to be an attractive method especially for outpatients due to its simplicity, safety, and low cost.[1,2] Intra-articular administration of local anesthesia during arthroscopic procedures has been used by many orthopedic surgeons,

also has been shown to provide effective analgesia after arthroscopic knee surgery.[1] A widely used local anesthetic for intra-articular injection is bupivacaine. Its prolonged duration of action makes it well suited for postoperative analgesia in this surgical population.[2,3] Nevertheless some side effects of bupivacaine have been reported, some of which are potentially serious: buccal and perioral paresthesias, impaired speech, convulsions, hemodynamic disorders, ventricular arrhythmias, even heart failure, hypersensitivity reactions, and urticaria.[4] Levobupivacaine is a new aminoamide local anesthetic. Although chemically related to bupivacaine, studies have shown levobupivacaine to produce less cardiac and central nervous system toxicity.[5] The effect of intra-articular 0.5% levobupivacaine has not been compared with the bupivacaine. The aim of this prospective, blinded and randomized study was to compare the analgesic effect and side effects of intra-articular levobupivacaine with bupivacaine after arthroscopic knee surgery.

Methods. After Institutional Ethics Committee approval and patients' written consent, 40 patients aged between 20-60 years, ASA I-II and undergoing elective knee arthroscopy were enrolled into the study protocol. Multiple arthroscopic procedures such as meniscectomy, excision of plicas, full arthroscopic lateral retinacular release, synovectomy, and chondral debridement were performed on the patients (**Table 1**) between January and June 2007 in Tepecik Education and Research Hospital, Izmir, Turkey. Exclusion criteria included a known allergy, sensitivity, or contra-indications to local anaesthetics, those who received preoperative opioids or any other analgesics in the preceding 48 hours.[6] All patients were visited before surgery and informed about the visual analog pain score (VAS) (0= no pain, 100= worst imaginable pain). Patients were unpremedicated and on arrival in the operating theatre all received a standardized general anesthesia. Anaesthesia was induced by intravenous (iv) administration of thiopental-sodium 5-6 mg/kg and fentanyl 1 µg/kg; endotracheal intubation was facilitated by iv administration of vecuronium bromide 0.1 mg/kg. Anaesthesia was maintained with 60% N_2O in oxygen and 2-3% sevoflurane. Monitorization included electrocardiography, non-invasive arterial blood pressure, and pulse oximetry (Nihon Kohden, Japan). No further opioids were administered intraoperatively. All operations and intra-articular injections were performed by the same surgeon. When the surgical procedure was completed, patients were assigned to one of the 2 groups (n=20 for each) in a blinded and randomized manner according to a computer generated table of random numbers. Group L received 20 ml 0.5% levobupivacaine (Nycomed Pharma AS, Elverum, Norway) and Group B received 20 ml 0.5% bupivacaine (AstraZeneca PLC, England), intra-articularly. Both orthopedic surgeons and anesthesiologists were blinded to the composition of the group in which each patients was included. Syringes with the solutions were prepared by the nursing staff and tagged with the name and number of each patient. After extubation, patients were observed in the post-anesthesia care unit for 2 hours and at orthopedic surgery ward by an anesthesiologist who was blinded to the groups.

Pain scores were recorded at 1, 2, 4, 6, 12, and 24 hours after intra-articular injection. Patients were not allowed to have a VAS score greater than 30 cm with rescue analgesic, such as diclophenac 75 mg (Voltaren 75 mg, Novartis) intramuscular (it was repeated every 12 h if needed), if the pain relief was insufficient after 30 minutes they were given tramadol 50 mg (maximum 4 times a day) orally. Total analgesic consumption (mg) at 24 hours and first analgesic requirement time which is considered as the time from intra-articular injection to the first requirement of diclofenac sodium were recorded. Patients were observed for nausea, vomiting, and any other side effects during the study period.

Statistical analysis was performed using the statistical Package for Social Sciences for Windows (SPSS version 10.0). Data are presented as mean±SD. Student t-test and Fisher's chi-square test were used, $p<0.05$ was accepted as significant.

Sample size was relatively low due to the availability of the data. So, the power of the statistical tests is low. Nevertheless, we accentuate only the statistically significant results, which do not depend so strongly on the sample size.

Table 1 - Distributions of surgical procedures.

Surgical procedures	Group L (n=20)	Group B (n=20)
Lateral retinacular release	12	13
Synovectomy	12	14
Meniscectomy	7	9
Chondral debridement	3	4
Excision of plica	20	20

Results. There were no significant differences between the 2 groups with respect to age, weight, gender of patients, and duration of surgery ($p>0.05$) (**Table 2**). Pain (VAS) scores are presented in **Table 3**. Although the VAS values of the patients treated with levobupivacaine tended to be lower than those of the other group, the differences were not statistically significant ($p>0.05$).

Analgesia duration and analgesia requirement are presented in **Table 4**. The first analgesic requirement times were not statistically different (p>0.05). Twelve patients in Group L (60%) and 9 patients in Group B (45%) needed no additional analgesic during 24 hours (p>0.05). There was no significant differences between groups with respect to total analgesic (diclofenac) consumption at 24 hours (78.7±70.8 mg versus 60.1±71.3 mg). No complications were found related to the intra-articular treatment.

Discussion. Infiltrating local anesthetics into the joint after the intervention has been one of the most widely used analgesic methods.[4] The mostly studied intra-articular local anesthetic agent was bupivacaine with its long duration of action.[3] The present study compared the postoperative analgesic effectiveness of levobupivacaine and bupivacaine with elective arthroscopic knee surgery under general anaesthesia. As a result, there were non-significant consistent differences between groups in VAS pain scores and analgesic consumption during 24 hours after surgery. Levobupivacaine is the levo-isomer of bupivacaine with a similar effect profile, but a documented reduced cardiac toxicity, as compared to traditional racimate bupivacaine and therefore a higher safety marginal.[7] Its use as a intra-articular analgesic has not been clinically compared to bupivacaine following knee surgery. In a study comparing the efficacy of levobupivacaine and lidocaine Jacobsoen et al[7] concluded that an intra-articular 0.5%

Table 2 - Demographic characteristics of the patient and duration of surgery

Demographic characteristics	Group L (n=20) (mean±SD)	Group B (n=20) (mean±SD)	*P* value	Mean difference	95% Confidence interval
Gender (M/F)	12/8	13/7	0.74		
Age (year)	37.8 ± 12.8	38.5 ± 14.2	0.87	0.7	-7.5 - 9.35
Weight (kg)	75.8 ± 11.6	78.9 ± 12.7	0.42	3.1	-4.69 - 10.89
Duration of surgery (minute)	57.8 ± 10.9	58.3 ± 11.8	0.89	0.5	-6.77 - 7.77
No statistically significant difference was found between groups.					

Table 3 - Pain scores of the patients (mm).

Time after surgery	Group L (n=20) (mean ± SD)	Group B (n=20) (mean ± SD)	P value	Mean difference	95% Confidence interval
One hour	18.6 ±12.4	21.4 ± 10.3	0.44	2.4	-4.5 - 10.1
Two hours	16.6 ± 10.7	18.9 ± 11.2	0.51	2.3	-4.71 - 9.31
Four hours	18.0 ± 11.9	19.2 ± 11.0	0.74	1.2	-6.14 - 8.54
Six hours	17.5 ± 12.3	18.8 ± 14.2	0.75	-0.3	-7.2 - 9.8
Twelve hours	18.3 ± 17.7	18.0 ± 15.2	0.95	-1.3	-10.86 - 10.26
Twenty-four hours	7.9 ± 7.1	9.2 ± 10.2	0.64		-4.33 - 6.93
No statistically significant difference was found between groups.					

Table 4 - Analgesia duration and analgesic requirements

Duration	Group L (n=20) (mean ± SD)	Group B (n=20) (mean ± SD)	*P* value	Mean difference	95% Confidence interval
Analgesia duration (min)	487.9 ± 89.1	474.4 ± 71.4	0.6	-13.5	-65.19 - 38.19
No. of patients requiring no analgesic	12	9	0.34		
No statistically significant difference was found between groups.					

levobupivacaine is effective analgesia knee arthroscopy. In studies comparing intra-articular bupivacaine with placebo, intra-articular bupivacaine was found to reduce pain scores and supplementary analgesic consumption to 10-50% in the early postoperative period up to 6 hours.[1,8-10] In studies with improved pain control, the mean dose of intra-articular bupivacaine was 90 ± 34 mg administered in concentrations of 0.25-0.5% in volume between 20 and 40 ml.[1] The dose of bupivacaine used for intra-articular instillation is important for effectiveness and duration of analgesia. In a study comparing the efficacy of bupivacaine and placebo Chirwa et al[11] concluded that an intra-articular 20 ml of 0.25% bupivacaine is effective at calming pain for a short period of approximately 2 hours. While Joshi et al[8] demonstrated that 25 ml of 0.25% bupivacaine provided analgesia for 4 hours and Eti et al[12] found that 20 ml of 0.5% bupivacaine decreased pain scores and the mean analgesic duration was 444.16±64.8 min. In our study, it was demonstrated that intra-articular bupivacaine (20 ml 0.5%) provided longer analgesia with a mean duration of 474.4±71.4 min. Also, in our study, the lack of a placebo group may of course be questioned; however, according to the results of studies intra-articular bupivacaine is accepted to provide reliable analgesia of predictable duration following knee arthroscopy and therefore it is also a valid active control as in our study protocol.

The clinical significance of the present study may be argued. Toxicity in conjunction with arthroscopy may not be a major risk, but risk-minimization is of importance especially in day-case surgery.[7] However Sullivan et al[13] reported 2 cases of cardiac toxicity after intra-articular injection of bupivacaine in doses of 75 and 150 mg which was reported as pharmacologically safe since the highest peak plasma concentration after 20 min was 0.625 ±0.225 µg/ml. Also Liguori et al[2] reported a case of possible local anesthetic toxicity secondary to intra-articular bupivacaine administration after arthroscopic surgery of the knee. In human being volunteers, intravenous levobupivacaine was associated with significantly less reduction in mean stroke index, acceleration index and ejection fraction than intravenous rasemic bupivacaine.[14] There have been case reports of CNS toxicity after administration of levobupivacaine for epidural, axillary and lumbar plexus blockade. However, no cardiovascular complications occurred in these patients.[14] Although we observed similar side effects between the 2 groups, it must be taken in consideration that the sample size was small, so further investigation is needed with more patients. In the present study, the analgesic effects of intra-articular 20 ml 0.5% levobupivacaine were found to be effective. In the literature, there is a considerable controversy about the analgesic efficacy of administering intra-articular bupivacaine, as well as the possibility of potentially serious side effects, particularly at high doses. According to our results, we believe that administering levobupivacaine intra-articularly is a good alternative to the analgesic treatment of patients who undergo arthroscopic procedures.

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