ORIGINAL ARTICLE

Acta Orthop Traumatol Turc 2012;46(6):411-415
doi:10.3944/AOTT.2012.2856

Intra-articular levobupivacaine, lornoxicam and morphine analgesia after knee arthroscopy: a randomized, controlled trial

Önder ERSAN[1], Taylan AKKAYA[2], Emine ARIK[2], Yalım ATEŞ[1]

[1]Department of Orthopedics and Traumatology, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey;
[2]Department of Anesthesiology and Reanimation, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey

Objective: The aim of this study was to compare the analgesic effects of intra-articular levobupivacaine alone, intra-articular levobupivacaine in combination with lornoxicam, and intra-articular levobupivacaine in combination with lornoxicam and morphine on patients following arthroscopic surgery.

Methods: The study included 60 ASA 1 and 2 patients between the ages of 20 and 70 years, scheduled for elective arthroscopy. Patients were divided into three groups of 20 through a randomized, double-blind method. Group 1 received 50 mg of levobupivacaine intra-articularly, Group 2 received 50 mg of levobupivacaine plus 8 mg of lornoxicam, and Group 3 received 50 mg of levobupivacaine plus 8 mg of lornoxicam and 8 mg of morphine. Visual analog scale (VAS) data was collected prospectively for the first 24 postoperative hours.

Results: Group 2 showed statistically significant differences, especially in VAS values with movement at 0, 4, and 6 hours ($p<0.001$).

Conclusion: The combination of levobupivacaine and lornoxicam is superior to levobupivacaine alone and the addition of morphine does not improve VAS scores. It appears that the addition of additional drugs for more effective analgesia has its limits.

Key words: Knee arthroscopy; levobupivacaine; lornoxicam; morphine; postoperative analgesia.

Knee arthroscopy is one of the most commonly performed one-day surgeries. Insufficient postoperative pain relief is one of the main reasons for continued hospitalization and delay in early rehabilitation. As a gold standard for pain relief has not yet been established, different drug combinations and administration methods are frequently investigated. Multimodal analgesia has become more commonly used in different surgical operations.[1-5] The use of different drugs to act in synergy and limit the side effect of any single drug used at a high-dose appears logical.[6]

We aimed to investigate the effect on postoperative analgesia and patient comfort of a combination of a local anesthetic, non-steroidal anti-inflammatory drug (NSAID) and opioid.

Patients and methods

Approval was obtained from the hospital ethics committee. A minimum sample size of 51 subjects (17 per group) was required to detect at least a 2-point difference in visual analog scale (VAS) scores between base-

Correspondence: Önder Ersan, MD. Dışkapı Yıldırım Beyazıt E.A.H., Ortopedi ve Travmatoloji Kliniği, İrfan Baştuğ Cad., Dışkapı, Ankara, Turkey.
Tel: +90 312 - 596 22 73 e-mail: onersan@gmail.com

Submitted: March 15, 2012 **Accepted:** August 27, 2012

Available online at
www.aott.org.tr
doi:10.3944/AOTT.2012.2856
QR (Quick Response) Code:

line and other measurement times, with a power of 80% at the 5% significance level. The difference of 2-points was taken from both the pilot study and clinical experience.[1]

Sixty ASA 1 and 2 patients between the ages of 20 and 70, scheduled for elective arthroscopy were enrolled in the study. Patients with additional pathology with the exception of meniscal tears, such as ligament tears or chondral lesions, patients that required more than two portals or those that had iatrogenic chondral damage during arthroscopy, pregnant women, patients that received other NSAIDs or antiaggregants in the 7 days before operation, patients allergic to one of the study drugs, and those with alcohol or drug abuse were not included in the study group. Additionally, patients with additional pathologies requiring intervention or requiring a tourniquet time more than 30 to 60 minutes during surgery were also excluded.

Patients were placed into 3 equal groups randomly, with the selection of an envelope in which the group and drugs to be given were written. Envelopes were opened by the pharmacist who was going to prepare the drugs for injection; the patient name was written on the paper and stored for later evaluation. If any patient was discontinued from the study, a new envelope was added to the stack containing the necessary information.

All patients were preoperatively evaluated for baseline value and accustomed to pain measurement. Measurements of pain at rest, at 90 degrees of flexion, and when walking on level ground were performed using the non-interrupted, 10-cm VAS.

Patients were premedicated with intramuscular midazolam 45 minutes before surgery. After entering the operating theater, standard monitoring with ECG, blood pressure and peripheral oxygen saturation was performed. After intravenous access, induction of anesthesia was performed using 2 mg/kg of propofol, 1 mg/kg of fentanyl, and 0.2 mg/kg of atracurium. All patients received a laryngeal mask airway and ventilation was performed with 100% oxygen. Anesthesia was continued with 40% of oxygen, 60% of N_2O, and 2% of sevoflurane.

Tourniquets were used in all patients with a pressure of 250 to 300 mmHg during surgery.

Group 1 patients (n=20) received levobupivacaine, Group 2 (n=20) received levobupivacaine + lornoxicam, and Group 3 (n=20) received levobupivacaine + lornoxicam + morphine. The drugs were prepared in a separate room and given to the surgical team at the end of the operation.

After the end of the operation and before deflation of the tourniquet, half of the dose was administered around the portals and the remaining dose was administered intra-articularly. A total volume of 20 ml was given to each patient. Group 1 received 10 ml of levobupivacaine (5 mg/ml) diluted with 10 ml of saline, Group 2 received 10 ml of levobupivacaine (5 mg/ml), plus 2 cc of lornoxicam (8 mg) with 8 ml of saline, and Group 3 received 10 ml of levobupivacaine (5 mg/ml), plus 2 cc of lornoxicam (8 mg), plus 2 cc of morphine (8 mg) with 6 ml of saline. To make a uniform injection, all patients received two 10 ml injections. In Group 1, the drug was divided into two injections and in Groups 2 and 3 one injection contained levobupivacaine only and the second contained the designated combination of drugs.

All arthroscopic surgeries and drug injections were performed by the same surgeon and all preoperative and follow-up VAS measurements taken by the same anesthesiologist who was blinded to the administered drug.

Inhalation anesthetics were discontinued and patients were ventilated with 100% oxygen following the completion of surgery and all injections. Neuromuscular blockade was reversed with neostigmine (35-70 mcg/kg) and atropine (0.01-0.02 mg/kg). Patients were extubated after commencement of sufficient respiration. In the recovery room, all patients received a patient-controlled analgesia (PCA) unit. Tramadol (50 mg) was administered as a bolus when the patient awoke and the time of administration was accepted as 0. PCA was then started with a total dose of 500 mg of tramadol with a 20-minute lock-out period and 10 mg dose when required.

Follow-up was performed at 0, 2, 4, 6, 12, and 24 hours using the VAS. Pain was measured and recorded on resting and with movement of the knee from full extension to 90 degrees of flexion separately by an anesthesiologist blinded to the groups. Before discharge at 24 hours, patients were asked whether they had any problem with sleeping due to pain and discomfort of the knee, whether walking without pain was possible, and whether they needed assistance with walking or not. PCA use and the amount of drugs administered were recorded as well as the use of rescue drugs. All patients were asked whether they had symptoms attributable to drug administration, such as nausea, vomiting, gastrointestinal symptoms or urinary retention. Patients were asked whether they would want to have the same medications if they had to undergo the same operation again.

Statistical analysis and sample size estimation were performed using NCSS and PASS 2000 programs.

The non-parametric Kruskal-Wallis test was used to determine VAS differences between groups, drug consumption and dose and patient preference. Hourly VAS changes between and within groups were calculated with the chi-square test. P values of less than 0.05 were considered significant.

Results

Average age, weight, height and male-to-female ratio of patients in the three groups were similar (Table 1).

All patients underwent arthroscopic meniscectomy. The average duration of anesthesia was 40.05 minutes in Group 1, 34.75 minutes in Group 2, and 41.60 minutes in Group 3. The differences between groups was not statistically significant (p=0.144).

The PCA dose of tramadol was on average 125.5 (range: 0 to 460.0) mg in Group 1, 122.0 (range: 0 to 490.0) mg in Group 2 and 116.0 (range: 0 to 360.0) mg in Group 3. This difference was not statistically significant (p=0.992).

Resting VAS values decreased in a statistically significant way in Group 1 after the 4th hour, in Group 2 after the 4th hour, and in Group 3 from 2nd hour on when compared with preoperative values (p<0.001) (Table 2).

VAS values taken with movement of the knee was significantly lower in all groups when compared to preoperative values (p<0.001) (Table 3).

VAS values showed a significant difference between preoperative VAS values and postoperative follow-up values (p<0.05) but there was no significant difference

Table 1. Patient characteristics.

	Group 1 (n=20)	Group 2 (n=20)	Group 3 (n=20)
Mean weight (range) in kg	73.65 (55-85)	73.80 (60-82)	74 (72-84)
Mean height (range) in cm	170.05 (158-178)	171.20 (160-179)	172.10 (165-180)
Male/Female	9/11	11/9	12/8
Surgery type (meniscectomy)	20	20	20

Table 2. VAS values at rest.

Time	Group 1 Mean±SD	Group 2 Mean±SD	Group 3 Mean±SD	p§
Pre-op	4.65±2.34	4.55±2.56	4.85±2.68	0.025
0 hr	0.70±1.75*	1.45±2.09*	0.95±1.28‡	0.303
2 hrs	0.65±1.09	1.25±1.29	0.60±0.94†	0.100
4 hrs	0.40±0.82†	0.45±1.05†	0.80±1.06†	0.222
6 hrs	0.20±0.52†	0.50±1.15†	0.25±0.55†	0.851
12 hrs	0.10±0.45†	0.30±0.98†	0.15±0.37†	0.635
24 hrs	0.10±0.45†	0.05±0.22†	0.05±0.22†	0.999

*The difference between pre-op values is statistically significant (p<0.05). †The difference between pre-op values is statistically significant (p<0.001). ‡The difference between pre-op values is statistically significant (p<0.01). §Kruskal-Wallis test.

Table 3. VAS values with movement.

Time	Group 1 Mean±SD	Group 2 Mean±SD	Group 3 Mean±SD	p‡
Pre-op	6.60±1.90	7.00±2.43	7.30±2.18	0.505
0 hr	2.05±2.96*	2.70±2.79*	1.40±1.63*	0.464
2 hrs	2.00±1.78*	2.70±1.56†	1.55±1.39*	0.077
4 hrs	1.95±1.76*	1.90±1.52*	1.40±1.31*	0.529
6 hrs	1.80±1.73*	1.50±1.61*	1.00±1.17*	0.338
12 hrs	1.60±1.70*	1.35±1.75*	0.80±1.10*	0.313
24 hrs	0.85±1.60*	0.25±0.64*	0.30±0.57*	0.589

*The difference between pre-op values is statistically significant (p<0.001). †The difference between pre-op values is statistically significant (p<0.05). ‡Kruskal-Wallis test.

between groups at post-operative times (p>0.05) (Tables 2 and 3).

When pain was evaluated during walking on a flat surface, all groups showed a statistically significant difference between preoperative and postoperative values (p<0.05) but no significant difference postoperatively (p=0.198). There was also no significant difference regarding the need for assistance during walking (p=0.198).

Sleeping satisfaction was similar in all groups; 85% in Group 1, 80% in Group 2, and 85% in Group 3. The differences were not statistically significant (p=0.887).

Complications were noted as follows: nausea in one patient, nausea and vomiting in 4 patients in Group 1; urinary retention and nausea and vomiting in one patient each in Group 2; and nausea in one, and nausea and vomiting in one patient in Group 3. There were no other complications.

Discussion

Decreasing postoperative pain and increasing comfort is one of the main challenges in modern medicine. Local anesthetics, NSAIDs, opioids and even steroids alone or in combination are used to facilitate early discharge from one-day surgery. Effective pain treatment should decrease postoperative hospitalization and allow for early rehabilitation. Lower doses of different drugs are used to create a synergistic effect on pain and decrease the rate of complications and side effects. Due to the high number of available drugs and different dose regiments, no gold standard in local use of drugs has yet been established.

The use of levobupivacaine or other local agents is known and has been published in the literature. Similarly, the use of opioids in combination with a local agent has also been well-studied, yielding mixed results as to whether there is really a local effect or the effect is systematic even though the dose is low. To our knowledge, The use of an NSAID drug in addition to a local anesthetic utilizing levobupivacaine and an opioid has not been previously reported.

The intra-articular use of bupivacaine has been shown to be toxic to chondrocytes[7,8] and to decrease the number of chondrocytes without causing tissue loss.[9] Levobupivacaine is an isomer of bupivacaine with a higher safety profile and less toxicity to the heart and the central nervous system. No study regarding its use on chondrocytes has been published and its intra-articular utilization is also limited in the literature.

The use of NSAIDs for pain relief is an emerging idea. The anti-inflammatory effects are a positive addition to the analgesic effects and studies have pointed out NSAIDs' use in outpatient arthroscopic surgery.[10] Eren et al. reported intra-articular lornoxicam to be superior to bupivacaine and saline for postoperative pain relief in patients undergoing arthroscopy.[11] Results also showed better VAS values at the 24th hour when compared to hours 0, 2, and 4 in the lornoxicam group.

The local use of morphine has given good results in various studies,[12] and its addition to a local anesthetic and an NSAID has also been shown to be effective.[12-14] However, in the current study, the addition of morphine did not decrease VAS values as expected. Joshi et al. also commented that, when given in combination with a local anesthetic, the addition of morphine did not increase the effectiveness of the analgesia.[15] Recently, studies have failed to show intra-articular multimodal drug injections to be superior to saline in relieving pain or increasing patient satisfaction or early ROM.[16,17]

In conclusion, the addition of the NSAID lornoxicam is superior to levobupivacaine alone for pain relief following outpatient arthroscopic surgery while the addition of morphine does not improve VAS scores. It appears that the addition of other drugs for more effective analgesia has its limits.

Conflicts of Interest: No conflicts declared.

References

1. Jacobson E, Assareh H, Cannerfelt R, Anderson RE, Jakobsson JG. The postoperative analgesic effects of intra-articular levobupivacaine in elective day-case arthroscopy of the knee: a prospective, randomized, double-blind clinical study. Knee Surg Sports Traumatol Arthrosc 2006;14:120-4.
2. Talu GK, Özyalçın S, Koltka K, Ertürk E, Akıncı Ö, Aşık M, et al. Comparison of efficacy of intraarticular application of tenoxicam, bupivacaine and tenoxicam-bupivacaine combination in arthroscopic knee surgery. Knee Surg Sports Traumatol Arthrosc 2002;10:355-60.
3. Leykin L, Nespolo R, Foltran F, Burato L, Noal N, Baciarello M, et al. Anesthesia and postoperative analgesia after intra-articular injection of warmed versus room- temperature levobupivacaine: a double-blind randomized trial. Arthroscopy 2009;25:1019-24.
4. Akkaya T, Ersan O, Ozkan D, Sahiner Y, Akin M, Gümüş H, et al. Saphenous nerve block is an effective regional technique for post-menisectomy pain. Knee Surg Sports Traumatol Arthrosc 2008;16:855-8.
5. Allen GC, St Amand MA, Lui AC, Johnson DH, Lindsay MP. Postarthroscopy analgesia with intraarticular bupivacaine/morphine. A randomized clinical trial. Anesthesiology 1993;79:475-80.
6. Izdes S, Orhun S, Turanli S, Erkilic E, Kanbak O. The effects of preoperative inflammation on the analgesic efficacy of intraarticular piroxicam for outpatient knee arthroscopy. Anesth Analg 2003;97:1016-9.
7. Gomoll AH, Yanke AB, Kang RW, Chubinskaya S, Willams JM, Bach BR, et al. Long-term effects of bupivacaine on cartilage in a rabbit shoulder model. Am J Sports Med 2009;37:72-7.

8. Nole R, Munson NM, Fulkerson JP. Bupivacaine and saline effects on articular cartilage. Arthroscopy 1985;1:123-7.
9. Chu CR, Coyle CH, Chu CT, Szczodry M, Seshadri V, Karpie JC, et al. In vivo effects of single intra-articular injection of 0.5% bupivacaine on articular cartilage. J Bone Joint Surg Am 2010;92:599-608.
10. Jacobson E, Assareh H, Cannerfelt R, Renström P, Jakobsson J. Pain after elective arthroscopy of the knee: a prospective, randomised study comparing conventional NSAID to coxib. Knee Surg Sports Traumatol Arthrosc 2006;14:1166-70.
11. Eren M, Koltka K, Talu GK, Aşık M, Özyalçın S. Comparison of analgesic activity of intraarticular lornoxicam, bupivacaine and saline after knee arthroscopy. [Article in Turkish] Agri 2008;20:17-22.
12. Ng HP, Nordström U, Axelsson K, Perniola AD, Gustav E, Ryttberg L, et al. Efficacy of intra-articular bupivacaine, ropivacaine, or a combination of ropivacaine, morphine, and ketorolac on postoperative pain relief after ambulatory arthroscopic knee surgery: a randomized double-blind study. Reg Anesth Pain Med 2006;31:26-33.
13. Akinci SB, Saricaoğlu F, Atay OA, Doral MN, Kanbak M. Analgesic effect of intra-articular tramadol compared with morphine after arthroscopic knee surgery. Arthroscopy 2005; 21:1060-5.
14. Ateş Y, Kinik H, Binnet MS, Ateş Y, Çanakçi N, Keçik Y. Comparison of prilocaine and bupivacaine for postarthroscopy analgesia: a placebo-controlled double-blind trial. Arthroscopy 1994;10:108-9.
15. Joshi GP, McCarroll SM, O'Brien TM, Lenane P. Intraarticular analgesia following knee arthroscopy. Anesth Analg 1993;76:333-6.
16. Joo JH. Park JW, Kim JS, Kim YH. Is intra-articular multimodal drug injection effective in pain management after total knee arthroplasty ?A randomized, double-blinded, prospective study. J Arthroplasty 2011;26:1095-9.
17. Rosaeg OP, Krepski B, Cicutti N, Dennehy KC, Lui AC, Johnson DH. Effect of preemptive multimodal analgesia for arthroscopic knee ligament repair. Reg Anesth Pain Med 2001; 26:125-30.