

# The Preemptive Analgesic Effect of Intraarticular Bupivacaine and Morphine After Ambulatory Arthroscopic Knee Surgery

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Intraarticular (IA) morphine provides effective postoperative analgesia after arthroscopic knee surgery. Some investigators have suggested that the preemptive administration of opioids may reduce postoperative analgesic requirements and hypersensitivity. We evaluated the analgesic effect of administering IA morphine either before or after surgical incision in patients undergoing arthroscopic knee surgery under local anesthesia. Forty patients undergoing arthroscopic meniscectomy were randomized into two groups. All patients received IA bupivacaine 0.25% before and after surgery together with IV sedation using midazolam and propofol. The Preemptive IA Morphine group received a single 3-mg dose of morphine with their preoperative bupivacaine. The Post-IA Morphine group received 3 mg

of morphine at the completion of surgery with the postoperative bupivacaine. After surgery, pain scores, the time to first opioid use, and 24-h analgesic use were recorded. Analgesic duration, defined as the time from completion of surgery until first opioid use, was significantly longer in those patients receiving preoperative ( $953 \pm 209$  min) versus postoperative ( $556 \pm 121$  min) IA morphine. The 24-h acetaminophen and oxycodone use was less in the Preemptive group ( $2.2 \pm 1.2$  pills) versus the Postoperative group ( $3.0 \pm 1.2$  pills). We conclude that IA morphine provides a longer duration of postoperative analgesia with less 24-h opioid use when administered before surgery.

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**C**linical evidence suggests that surgical trauma may induce prolonged changes in both the peripheral and central nervous system (CNS), which together amplify postoperative pain (1). Peripheral sensitization seems to occur through a reduction in the threshold of nociceptor afferent peripheral terminals, whereas an activity-dependent increase in the excitability of spinal neurons underlies the shift to CNS hypersensitivity (1). Preemptive analgesia involves the administration of analgesics before painful stimuli. This prevents the establishment of a hypersensitized state and, thus, the amplification of postoperative pain. McQuay et al. (2) revealed a significant

prolonged analgesic duration and a reduction in postoperative analgesic use when opiates were administered before surgery in patients undergoing orthopedic surgery.

Numerous clinical trials examining the local analgesic effects of intraarticular (IA) morphine have been published in the last 10 yr (3–10). Although some report equivocal analgesia (3), most clinical investigations support the analgesic efficacy of IA opioids (4–10). In fact, several of these studies have revealed prolonged postoperative analgesia for up to 24 h after a single IA morphine injection following arthroscopic knee surgery. In all of these clinical investigations, however, morphine was administered at the completion of the surgical procedure. We hypothesized that IA morphine may be more effective if administered in the preoperative rather than the postoperative period.

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## Methods

After approval by the local IRB, informed consent was obtained from 40 patients scheduled to undergo elective

arthroscopic meniscectomy of the knee. All patients received 30 mL IA bupivacaine 0.25% 30 min before surgery. Subsequently, patients were assigned in a randomized, double-blinded manner into two groups: Group 1 received IA morphine 3 mg with their preoperative bupivacaine, and Group 2 received IA morphine 3 mg with their postoperative bupivacaine. All solutions were prepared by an anesthesiologist who was otherwise not involved in the case. During surgery, patients received IV sedation with midazolam (1–3 mg) and propofol ( $10\text{--}100\ \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ). An additional 30 mL bupivacaine 0.25% was injected through the arthroscope at the end of the case. No opioid analgesics were administered during surgery.

Postoperative pain was assessed with an 11-point verbal analog scale (VAS), with 0 corresponding to no pain and 10, the worst imaginable pain. VAS pain scores were recorded both at rest and with movement at 1, 2, and 24 h after the completion of surgery. Patients were instructed to take one or two acetaminophen 325 mg and oxycodone 5 mg tablets every 3 h as needed for a pain VAS score  $\geq 3$  while at home. When contacted by telephone at 24 h, patients were asked about their time to first analgesic use, as well as their 24-h total requirement. Analgesic duration was defined as the time from completion of surgery until the first request for acetaminophen and oxycodone. Patients were discharged from the hospital when they were oriented to time and place, were able to void, had stable vital signs, and could ambulate with the assistance of crutches. Discharge time was classified as the time from the end of surgery until the patients were able to meet these discharge criteria.

A power analysis was performed for a power of 0.9 and an  $\alpha$  of 0.05 with the following assumptions: duration of preemptive IA morphine analgesia of  $570 \pm 120$  min and a postoperative IA morphine analgesic duration of  $450 \pm 120$  min. This yielded a sample size of 18 per group. Demographic data were analyzed as continuous normal data: an unpaired *t*-test was used. Sex was analyzed by using contingency analysis and the  $\chi^2$  test. Data on timed variables were analyzed nonparametrically because of the bounded nature of the data: a Mann-Whitney *U*-test was used to determine significance. Pain scores and the amount of postoperative analgesics, because of the ordinal and discrete nature of the data, were analyzed with a Mann-Whitney *U*-test. Data are presented as mean  $\pm$  SD. Significance was determined at  $P < 0.05$ . Statistical evaluations were performed with StatView 5.0 (SAS Institute, Inc., Cary, NC).

## Results

Intraoperative local anesthesia provided satisfactory conditions for all patients undergoing surgery. There

were no significant differences between the two groups with respect to age, sex, height, weight, duration of surgery, or the time to discharge (Table 1). There was no significant difference in VAS pain scores recorded at rest or with movement at 1, 2, and 24 h after surgery (Table 1).

There was a significant difference with respect to the analgesic duration between the two groups ( $P < 0.001$ ). Patients in Group 1, who had received preoperative IA morphine, experienced a longer interval ( $953 \pm 209$  min) before taking postoperative analgesics compared with those patients in Group 2 who received postoperative IA morphine ( $556 \pm 121$  min).

The 24-h consumption of acetaminophen and oxycodone tablets was also significantly different between the two groups ( $P = 0.02$ ). Patients in Group 1 required fewer tablets ( $2.2 \pm 1.2$ ) compared with Group 2 ( $4.0 \pm 1.2$ ).

## Discussion

Our study revealed that IA morphine is more effective when administered in the preoperative versus postoperative period in patients undergoing arthroscopic meniscectomy. This was evidenced by a longer analgesic duration, as well as a reduced requirement for acetaminophen and oxycodone tablets during the first 24 hours after surgery. The similar pain scores at one and two hours may reflect the ability of IA bupivacaine to provide effective postoperative analgesia for two to four hours after this surgery (11).

Experimental research indicates that locally administered opioid agonists can produce analgesic effects by binding with peripheral opioid receptors (12). All three opioid receptor types ( $\mu$ ,  $\delta$ , and  $\kappa$ ) have been isolated on peripheral nerves, and each was shown to be a possible site for mediating peripheral antinociception (13). More recently, opioid receptors have been found in synovial biopsies from the knee (14). Stein et al. (5) showed that small doses (1 mg) of IA morphine significantly decreased postoperative pain after arthroscopic knee surgery and was blocked by IA naloxone, suggesting a peripheral analgesic effect. After this study, numerous clinical investigations have reported effective and long-lasting analgesia from small IA doses of morphine (6–10). In all of these clinical studies, however, IA morphine was administered at the conclusion of the surgical procedure. This study demonstrates that the preoperative IA administration of this opioid is more effective.

The results of this study are consistent with findings in animal studies, which revealed that the administration of opioid analgesics before noxious stimulation can prevent or significantly reduce the prolonged hyperexcitability that occurs in the CNS (15,16). In a study by Woolf and Wall (15), the dose of systemically

**Table 1.** Patient Demographics, Surgical Data, and Pain Scores

Group <sup>a</sup>	n	Age (yr)	Weight (kg)	Height (cm)	Duration of surgery (min)	Discharge time (min)	1-h		2-h		24-h	
							Rest	Movement	Rest	Movement	Rest	Movement
1	20	44 ± 10	71 ± 12	169 ± 9	49 ± 8	89 ± 15	2.2 ± 1.0	2.9 ± 0.7	2.8 ± 0.7	3.2 ± 0.7	3.2 ± 0.7	3.7 ± 0.5
2	20	48 ± 13	74 ± 13	164 ± 10	46 ± 8	98 ± 14	2.3 ± 0.9	2.9 ± 0.9	2.9 ± 0.7	3.5 ± 1.1	3.3 ± 0.8	3.6 ± 0.6

Data are presented as mean ± sd.

<sup>a</sup> There were no significant differences between the two groups.

Group 1 = intraarticular morphine 3 mg administered before surgery; Group 2 = intraarticular morphine 3 mg administered after surgery.

administered morphine needed to prevent the establishment of central hyperexcitability before trauma was one-tenth the dose required to abolish the prolonged activity once it had developed. In a large retrospective study of patients undergoing orthopedic surgery, McQuay et al. (2) revealed a significant reduction in postoperative pain medication requirements when opioid analgesics were administered in the preoperative period. This study also revealed that a significantly larger number of patients (12%) in the opioid premedication group never required analgesics compared with the unpremedicated group (5%). The use of preemptive opioids was also beneficial in patients undergoing lumbar disk surgery, increasing the first analgesic request, decreasing the number of patients requiring postoperative analgesics, and decreasing 48-hour opiate requirements (17). The use of preemptive opioids is effective in reducing postoperative pain after abdominal hysterectomy surgery (18), in addition to orthopedic surgery.

It might be expected that administering IA morphine before surgery may be ineffective because of a possible washout of the drug during the intraoperative IA lavage. However, by administering IA morphine at least 30 minutes before incision, effective opioid receptor binding can be achieved. In fact, Lundin et al. (19) demonstrated that bupivacaine and morphine injected IA only 20 minutes before the start of knee surgery provided more effective postoperative analgesia than bupivacaine alone. It might be instructive to vary the time to explore the optimal timing of the administration of IA morphine.

This study design can be criticized because the preemptive analgesic effect of morphine was evaluated when combined with bupivacaine rather than saline or bupivacaine alone (20). Although local anesthetics may also have a preemptive analgesic effect (21), a study group with IA bupivacaine alone was not included, because our previous studies failed to reveal an analgesic duration of more than four hours when administered for the same surgical procedure (22,23). The administration of opioids, when combined with local anesthetics, enhances postoperative analgesia by a peripheral mechanism (21,24,25). Morphine can enhance the local anesthetic effect of bupivacaine (21,24) and may prolong the blockade of peripheral nociceptive input from the surgical site of trauma. We also

chose not to use IA saline alone, because this would require our patients do undergo general anesthesia, which is not our current standard of practice. The potential benefits of performing outpatient knee arthroscopy under local anesthesia, compared with general anesthesia, include less cost, decreased incidence of postoperative nausea and vomiting, earlier discharge, and earlier mobilization (26,27). Jacobson et al. (27) demonstrated that outpatient knee arthroscopy can be performed effectively and safely under local anesthesia and recommended its preference over general anesthesia.

In conclusion, IA morphine provides more effective postoperative analgesia when administered before surgery rather than at the end of surgery. This study supports the preemptive analgesic effect of IA morphine for arthroscopic meniscectomy performed under local anesthesia.

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