Comparison of Postoperative Analgesic Effects of Intraarticular Bupivacaine and Morphine Following Arthroscopic Knee Surgery

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Recent studies have shown that, in the presence of inflammation, the local administration of opioids results in analgesia. The analgesic efficacy of local anesthetics and morphine administered intraarticularly was compared in patients undergoing arthroscopic knee surgery under epidural anesthesia. We compared postoperative pain scores (VAS) and opioid requirements among 47 patients receiving, in a randomized, double-blinded fashion, one of three intraarticular medications (20 ml): normal saline with 100 μg epinephrine (group 1, n = 16); 0.25% bupivacaine with 100 μg epinephrine (group 2, n = 15); and 3 mg morphine sulfate and 100 μg epinephrine in normal saline (group 3, n = 16). VAS scores were similar in the groups preoperatively and on arrival in the recovery room. At the end of the first postoperative hour, the residual sensory blockade was minimal in all three groups (mean = 3.9–4.1 segments) and almost total recovery occurred in all three groups before the second postoperative hour. The VAS in group 3 was not significantly different than group 1 at any time interval. Intraarticular bupivacaine (group 2) provided significantly better analgesia than did saline or morphine (group 1 or 5) in the first 2 postoperative hours (ANOVA, P < .05). Subsequent VAS scores were not significantly different in the three groups. While no patient in group 2 requested analgesics during the first postoperative hour, nine patients in group 3 required systemic analgesics (P < .01). We conclude that no evidence for a peripheral opioid-receptor mediated analgesia could be demonstrated in patients undergoing arthroscopic knee surgery under epidural anesthesia. (Key words: Analgesics, opioid: morphine. Anesthetics, local: bupivacaine. Pain: postoperative. Receptors: opioid. Surgery: arthroscopy.)

The recent growth in outpatient surgery has presented new challenges in the field of postoperative pain management. Difficulties in adapting common methods of acute postoperative pain management in hospitalized patients to outpatients has resulted in inadequate treatment of pain following outpatient surgery.1,2 Thus, the search continues for an ideal analgesic technique that is site specific, long-lasting, easily administered and has a high therapeutic safety index.

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Arthroscopic surgery of the knee is a common outpatient procedure. Although intraarticular injection of bupivacaine following arthroscopy has been demonstrated to be safe3–5 and effective6,7 in providing postoperative analgesia, the mean duration of analgesia is only 2 h.7 In a recent report, an intraarticular morphine resulted in prolonged analgesia following arthroscopic knee surgery.8 Intraarticular injection of opioids theoretically has the potential to fulfill several of the above-listed criteria of an ideal analgesic following arthroscopy.

Contemporary research has focussed on “peripheral sites” in the region of tissue injury as potential targets of analgesic drugs. For example, the traditional view that opioids produce analgesia solely by action on opiate receptors in the central nervous system has been challenged by evidence for peripheral opiate receptor-mediated analgesia.9–12 Russell and coworkers13 demonstrated in an electrophysiologic study in cats that close arterial injection of opioids inhibited the spontaneous discharges of a majority of the small diameter afferents from inflamed knee joints in a dose-dependent manner. This effect was naloxone reversible, suggesting an opiate receptor-mediated mechanism.

The present study was designed to determine whether intraarticular administration of opiates results in postoperative analgesia following arthroscopic surgery. In addition, the analgesic effect of an intraarticular opioid was compared to that of local anesthetics.

Material and Methods

Patients (ASA physical status 1–3) scheduled for elective outpatient arthroscopic surgery of the knee performed by a single surgeon (C. A. J.) were enrolled in the study. The study protocol was approved by the Joint Committee on Clinical Investigation of The Johns Hopkins Medical Institutions. Informed consent was obtained from all patients. Patients younger than 18 yr or with cruciate ligament tears were not included in the study. Exclusion criteria were acute traumatic injury to the knee, the use of oral narcotics preoperatively, history of allergy to any study medication, and the refusal of epidural anesthesia. Surgical procedures were similar in the three groups and included debridement of fat pad and adhesions, synovectomies, and partial or total meniscectomies.
Patients did not receive any medication prior to coming to the operating room.

Patients were randomized prospectively to one of three groups. Patients were asked to mark the intensity of their ongoing knee pain on a 10-cm visual analog pain scale (VAS) prior to the start of the anesthetic. The VAS was anchored at 0 (no pain) and 10 (most intense pain). The VAS has been validated for both clinical and experimental pain by previous studies.\(^8\) The anesthetic regimen consisted of lumbar epidural anesthesia using 2% lidocaine hydrochloride with 1:200,000 epinephrine (range 13–20 ml). The mean dermatomal level of analgesia to pinprick was T10 (range T8–T12). Midazolam for sedation was titrated in increments of 1 mg (median dose 4 mg). Epidural and parenteral opioids were avoided pre- and intraoperatively. All patients underwent arthroscopic surgery after inflation of a thigh tourniquet to 300–350 mmHg.

At the conclusion of the procedure, the appropriate study drug was administered in a double-blinded, randomized manner from a coded syringe into the joint space via an 18-G needle. Patients in group 1 received 20 ml of normal saline and 100 \(\mu\)g epinephrine. Patients in group 2 received 20 ml 0.25% bupivacaine and 100 \(\mu\)g epinephrine, and patients in group 3 received 3 mg of preservative-free morphine and 100 \(\mu\)g epinephrine in a total volume of 20 ml of normal saline.

The tourniquet was deflated and the patient was taken to the postanesthesia recovery unit and subsequently to the Same Day Care Center prior to discharge. An observer blinded to the patients' group assignment obtained hemodynamic data, VAS scores, and noted the level of residual epidural block upon arrival in the recovery unit and each hour until discharge (3–6 h). The observer also recorded the time at which the patient first requested pain medication. Analgesic therapy in the immediate postoperative period was managed by a physician not directly involved in the study. The usual analgesic regimen was oral Tylox\(^*\) (5 mg oxycodone hydrochloride and 500 mg acetaminophen, McNeil Pharmaceuticals, Fort Washington, PA). If pain was uncontrolled with oral opioids, iv fentanyl was administered with an initial bolus dose of 50 \(\mu\)g and additional doses titrated as needed.

All patients were discharged home with 20 capsules of Tylox and a supply of VAS sheets. Patients were advised to take their analgesic medication on a 4-h as-needed basis and rate their pain intensity on the VAS scale at 6-h intervals. Patients were seen at follow-up by the surgeon at 48 or 72 h, at which time a final VAS was completed, the number of unused Tylox capsules counted, the average 24-h use of opioid calculated, and the presence of any complications ascertained.

### Statistics

A one-way analysis of variance was used to compare pain scores in the three groups, and the least significant difference method used for pairwise comparisons of means at each time point (Statistix v3.1, Analytical Software, St. Paul, MN). The time to first analgesic dose and the 24-h analgesic requirement were analyzed using a one-way analysis of variance. A chi-square analysis of contingency table was used for comparison of categorized data such as ASA physical status and gender. Results are shown as mean ± SEM. A \(P\) value of < .05 was considered to be statistically significant.

### Results

Forty-nine patients were enrolled in the study; one patient was lost to follow-up, and one patient was too sedated in the recovery unit to obtain measurements of postoperative pain. Data from these two patients were excluded from further analysis. There were no significant differences among the groups in ASA physical status, gender, height, or weight. The male/female ratios were similar in the three groups (M:F = 11:5, 12:3, 12:4 in groups 1, 2, and 3, respectively). Additional patient demographics, anesthetic doses, surgical time, and times for recovery from the epidural anesthetic for the 47 patients included in the study are given in table 1. No significant differences

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between the groups in any of the above-mentioned parameters (ANOVA, \( P > .05 \)) were observed.

The preoperative and postoperative VAS scores during the first 6 h after surgery for the three groups are shown in figure 1. The difference in group scores are significant at the first and second postoperative hours. There are no other significant differences throughout the postoperative period. The lower number of patients during the sixth postoperative hour reflects that most patients were discharged prior to that time. The 24- and 48-h VAS scores were 2.2 \( \pm \) 0.6 and 1.9 \( \pm \) 0.6 in group 1, 1.9 \( \pm \) 0.6 and 1.5 \( \pm \) 0.3 in group 2, and 2.2 \( \pm \) 0.5 and 1.9 \( \pm \) 0.6 in group 3 \( (P > .05) \).

Patients in group 3 (morphine) requested pain medication earlier than those in group 2 (bupivacaine; \( P < .01 \); table 2). Nine of 16 patients in the morphine group (group 3) and 2 of 16 patients in the control group (group 1) required supplemental analgesics during the first postoperative hour \( (P < .05) \). In contrast, none of the patients in the bupivacaine group required analgesics during the same hour \( (P < .01 \) compared to group 3). Despite the additional analgesic use in the morphine group, the VAS scores during the first 2 postoperative hours were higher in this group of patients compared to patients in the bupivacaine group \( (P < .05 \); fig. 1). Patients took pain medication \textit{ad lib} over the first 2–3 postoperative days until follow-up. The Tylox\textsuperscript{®} consumption per day did not differ by group (table 2).

Complications included two hematomas in each of the bupivacaine and morphine groups that resolved with either aspiration or conservative therapy and resulted in no long term sequelae.

**Discussion**

Our results indicate that, in patients undergoing arthroscopic knee surgery under regional anesthesia, intraarticular bupivacaine results in analgesia in the immediate postoperative period. In contrast, intraarticular morphine failed to provide significant analgesia during the same period. Our results are in agreement with those of earlier studies on the effects of intraarticular local anesthetics on postoperative analgesia in patients undergoing arthroscopy under general anesthesia.\textsuperscript{7,15–17} Our observations of a lack of analgesic effect of morphine during the first 2 postoperative hours are also similar to the observations of Stein et al.\textsuperscript{8} However, unlike in the reports of Stein et al.\textsuperscript{8} and Khoury et al.,\textsuperscript{17} we failed to observe a prolonged or perhaps delayed and prolonged analgesic effect with morphine. Our results are in agreement with those of Heard et al.,\textsuperscript{18} who failed to demonstrate significant postoperative analgesia following intraarticular morphine in patients undergoing arthroscopic surgery either under general or regional anesthesia. The reasons for the discrepancy between the studies are not clear at present, but possible explanations are discussed.

Opiate receptors and endogenous opiates have been demonstrated not only in brain and spinal cord but in peripheral nerves and the dorsal root ganglia.\textsuperscript{19,20} Neurophysiologic studies in uninjured skin have, however, failed to demonstrate an effect of opiates on response of cutaneous nociceptive afferent fibers innervating normal tissues.

### Table 2. Postoperative Opioid Requirements

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (Saline)</th>
<th>Group 2 (Bupivacaine)</th>
<th>Group 3 (Morphine)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n )</td>
<td>Mean ( \pm ) SEM</td>
<td>( n )</td>
<td>Mean ( \pm ) SEM</td>
</tr>
<tr>
<td>Time to first opioid dose (h)</td>
<td>13</td>
<td>2.9 ( \pm ) 0.7</td>
<td>11</td>
<td>5.7 ( \pm ) 1.6*</td>
</tr>
<tr>
<td>No. of opioid tablets per day</td>
<td>15</td>
<td>3.0 ( \pm ) 0.6</td>
<td>14</td>
<td>2.5 ( \pm ) 0.6</td>
</tr>
</tbody>
</table>

* Group 2 significantly greater than groups 1 and 3 \( (P < .01) \); group 3 not different from group 1 \( (P > .05) \).
skin in cat and monkey. Several behavioral studies have demonstrated a site-specific analgesia by peripherally administered opioids in models of peripheral inflammation in rats. It is possible that the activation of the peripheral opiate receptors depends on the presence of chemical mediators of inflammation. Behavioral and pharmacologic studies suggest a peripheral site of action of opioids in inflamed tissue. Joris et al. demonstrated that ethylketocyclazocine, a kappa opiate receptor agonist, and fentanyl, a mu receptor agonist, when injected subcutaneously blocked the thermal hyperalgesia induced by local inflammation of carrageenan in the rat paw. The same doses of opiate had no effect when given systemically. Opiates also inhibit cutaneous vasodilatation and extravasation induced by antidromic nerve stimulation by inhibiting neuropeptide release from the sensory terminals. In addition, the peripheral release of substance P following C-fiber-strength stimulation of the peripheral nerve can be blocked by opioids. The presence of periaxial opiate receptors also has been demonstrated in neurophysiologic studies in the cat following a chemically induced inflammation.

Two possible explanations could account for the discrepancy between the results of this study and the recent reports of Stein et al., who observed a delayed, but prolonged, analgesic effect with intraarticular morphine. All patients in this study, including the control group, had intraarticular injection of epinephrine. If the local presence of epinephrine altered the inflammatory process, and thereby interfered with the activation of the opiate receptors, a peripheral opiate-receptor mediated analgesia may have been masked in our study. A second, more intriguing possibility pertains to the different anesthetic regimens in the two studies. Patients in this study underwent arthroscopy with epidural anesthesia, in contrast to the study by Stein et al., in which patients had general anesthesia. If the activation of the peripheral opiate receptors depends on neuroendocrine responses secondary to the afferent barrage of impulses along nociceptive pathways, epidural anesthesia may prevent this activation. Recent reports indicate that protecting the nervous system from the noxious insults of surgery, by using regional analgesic techniques, results in blunting of the neuroendocrine response and confers long-term reduction in pain. Thus, if the activation of peripheral opiate receptors is critically dependent on input to the central nervous system along nociceptive afferents, our anesthetic regimen would have precluded a peripheral opiate-receptor mediated analgesia. The observations by Heard et al. that the patients who had regional anesthesia had lower VAS scores, irrespective of intraarticular drug treatment, compared to patients undergoing similar arthroscopic procedures under general anesthesia adds credence to this hypothesis.

The mechanism by which intraarticular morphine is associated with higher pain scores in the immediate postoperative period is obscure. Local histamine release or differences in pH may be contributory, though these factors were not analyzed in this study. However, increase in pain during the first 2 hours following arthroscopy was also observed by Khoury et al.

In conclusion, intraarticular bupivacaine provides better analgesia than does saline in the immediate postoperative period in this randomized prospective double-blind study. Our study fails to demonstrate functional opiate receptors in the knee joint in a clinical model of acute injury.

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