Intra-articular Morphine Versus Bupivacaine for Postoperative Pain Management

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Abstract

The purpose of this study was to determine whether morphine would be as effective as bupivacaine for postoperative pain control after knee arthroscopy with no worsening of the side effect profile. Eighty-two patients who underwent partial meniscectomy, chondral debridement, or both were prospectively randomized to receive 10 mg of morphine (10-cc volume) or 10 cc of 0.5% bupivacaine immediately postoperatively. Visual analog scale scores and side effect profiles were recorded in the postanesthesia care unit, in the transitional care unit, and then every 4 hours postoperatively until 24 hours. In-hospital data were available for all 82 patients, but postdischarge data were available for only 64 patients. Visual analog scale scores in the postanesthesia care unit decreased from 3.4 on admission to 2.4 on discharge for the morphine group and from 2.6 to 2.4 for the bupivacaine group (P>.217, all time points). Medication use was the same for both groups in the hospital (62% and 78%, respectively) with no statistical difference. Visual analog scale scores decreased from 3.0 to 1.5 for the morphine group and from 2.8 to 1.8 for the bupivacaine group between 4 and 24 hours postoperatively (P>.376, all time points). Medication use decreased between 4 and 24 hours postoperatively for both groups, from 71.7% to 52.9%, respectively, with no statistical difference at all time points. Four patients in the morphine group and 1 patient in the bupivacaine group experienced side effects. This study indicates that 10 mg of intra-articular morphine is as effective as 10 cc of 0.5% bupivacaine for postoperative pain control for partial meniscectomy and chondral debridement of the knee. It minimally increases side effects initially and circumvents the issue of chondral toxicity of bupivacaine.
Recent literature indicates that intra-articular administration of bupivacaine and lidocaine may harm hyaline cartilage. The harmful effects are time and dose dependent. For this reason, many surgeons inject only the portal sites. However, some surgeons still routinely inject these agents into the knee perioperatively and in the clinic setting for pain control.

Other agents have also been injected into the knee with good pain relief, including neostigmine, clonidine, morphine, and various anti-inflammatory agents. These agents may have a less detrimental effect. In particular, morphine is an opioid that acts on naturally occurring opioid receptors in the synovial lining of the knee and has been shown to be safe for human articular cartilage in vitro. Presumably, its safety profile is greater than that of lidocaine or bupivacaine in regard to articular cartilage toxicity.

This study compared the analgesic effects of intra-articular morphine with those of intra-articular bupivacaine for patients undergoing knee arthroscopy. Both agents have been proven to work, and both are still widely used. Some results indicate that bupivacaine is superior, whereas others conclude that morphine is superior for postoperative pain control. No clear-cut consensus exists. Existing studies describe various potential confounding methodologic factors, including variable dosing of administered medications, variable volumes of administration, variable surgical anesthetic protocols, variable use of tourniquets, use of postoperative drains, variety of procedures performed, and use of epinephrine. These variables contribute to the confusion as to which drug is more effective.

The current authors designed a clinically relevant protocol to compare the effects of intra-articular morphine and bupivacaine in the postoperative setting. They hypothesized that intra-articular morphine would be as effective as or more effective than bupivacaine at time points up to 24 hours postoperatively and would effectively manage postoperative pain. They also hypothesized that the side effect profile of morphine would be worse than bupivacaine but that the effect should be negligible. The purpose of the study was to validate the use of intra-articular morphine and provide an alternative to bupivacaine to avoid the potential harm to hyaline cartilage.

**Materials and Methods**

**Study Design**

The study was approved by the institutional review board. Patients undergoing arthroscopic partial meniscectomy with or without chondral debridement were prospectively randomly assigned to 1 of 2 methods for postoperative pain control. No placebo group was used for ethical reasons. Group assignment was determined by an odd or even account number given on the day of surgery. Odd numbers were given morphine, and even numbers were given bupivacaine. The patients were blinded to group assignment, but the investigators were not. The authors did not believe that the lack of investigator blinding would affect the patients’ rating of their postoperative pain in the first 24 hours postoperatively, which is the variable of interest, because the investigators had no contact with the patients in that period. Data were collected by 1 of the authors (V.K.), and the lead investigator (H.E.) was not involved with the data until final analysis.

**Patients**

Patients who consented to undergo arthroscopic meniscectomy with or without chondral debridement were invited to participate in this study. Exclusion criteria were (1) preexisting neurological disorder; (2) lower quadrant neuropathy; (3) planned use of epidural rather than general anesthesia; (4) known allergy to bupivacaine or morphine; (5) age of 17 years or younger (ie, all patients had to be 18 years or older); (6) chronic narcotic use; and (7) allergy to the pain medications. These exclusion criteria were reviewed by use of a checklist by the investigators at the time of recruitment and again by anesthesia staff immediately preoperatively. Potential patients received an explanation of the purpose and procedures of the study, and informed consent was obtained for each patient.

**Pre- and Intraoperative Procedures**

This study did not affect the current standard of care for pain management at the authors’ institution; both methods being investigated have been in common use, and available evidence suggests that both are effective for controlling postoperative pain.

All patients received general anesthesia for surgery using the following protocol. Patients were premedicated with 1 to 3 mg of midazolam as needed for anxiety. Induction was achieved using 0 to 50 µg of fentanyl as needed (maximum dose, 100 µg), 1 to 3 mg/kg of propofol titrated to effect, 1 to 1.5 mg/kg intravenous (IV) of lidocaine, and 4 mg IV of ondansetron as needed for nausea. Anesthesia was maintained with desflurane or sevoflurane adjusted for blood pressure and depth of anesthesia.

All procedures were performed by 1 fellowship-trained sports medicine surgeon (H.E.) with 10 years of experience performing more than 400 arthroscopic procedures per year. Of note, a chondral debridement for the surgeon involved simple removal of delaminating and fibrillated edges and margins of articular cartilage with no exposure of the calcified cartilage layer or subchondral bone.

The bupivacaine group received an intra-articular injection of 10 mL of 0.5% bupivacaine without epinephrine at the conclusion of the operative procedure after all arthroscopy fluid had been drained and the incisions were closed. The morphine group received an intra-articular injection of 10 mg of morphine (10 mg in 10 mL of lactated Ringer’s solution) at the
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Postoperative Pain Measurement

Pain was evaluated using the VAS and by medication use. Postoperative pain intensity was evaluated on admission and discharge from the postanesthesia care unit, admission and discharge from the progressive care unit, and every 4 hours through 24 hours postoperatively using the VAS.

The pain medication log was used by patients to record their medication intake. They also noted their pain level using the VAS at the time of medication intake. Patients indicated in the log whether they had experienced nausea or vomiting at any time in the 24-hour postoperative period.

Data and Analysis

The 2 groups were compared on several outcomes: peak pain, medication use, and occurrence of side effects (e.g., nausea, vomiting, dizziness, sedation, and itching). A longitudinal data analysis model was used to compare pain and medication use between the 2 methods. The frequency of side effects was compared between the 2 methods using chi-square analyses.

A power analysis was conducted at the beginning of the study to determine the sample size that would be necessary to detect a clinically meaningful difference between the 2 groups over time. A repeated measures analysis of variance (ANOVA) was used to detect a clinically meaningful difference between the 2 groups over time. A power analysis was conducted at the conclusion of the study to determine the sample size that would be necessary to detect a clinically meaningful difference between the 2 groups over time.

RESULTS

Eighty-two patients (32 women and 50 men) were randomized to either the morphine (n = 47; mean age, 54.3 ± 13.0 years) or bupivacaine (n = 35; mean age, 52.7 ± 13.2 years) group. The surgery types did not differ between study groups (P = .999) (Table 1). Most of the patients in both groups (91.3% and 88.2%, respectively) had a partial meniscectomy. Thirty patients had a partial meniscectomy alone, 43 patients had partial meniscectomy and chondral debridement (16 times [16 patients] involving the patella), and 9 patients had chondral debridement alone. Operative time, defined as the time from skin incision to completed dressing placement, did not differ between groups (mean, 25.6 ± 9.0 and 24.3 ± 8.0 min, respectively) (P = .530).

Eighteen patients (11 in the morphine group and 7 in the bupivacaine group) had data available through hospital discharge but no data in the subsequent 24 hours. The remaining 64 patients (36 in the morphine group and 28 in the bupivacaine group) had postanesthesia care unit data, as well as follow-up VAS and medication use data through 24 hours postoperatively. All available data were used in the follow-

### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Morphine Group</th>
<th>Bupivacaine Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average patient age, y</td>
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<td>52.7</td>
</tr>
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<td>Data recorded, No.</td>
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<td></td>
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<tr>
<td>In hospital</td>
<td>47</td>
<td>35</td>
</tr>
<tr>
<td>24 h postop</td>
<td>36</td>
<td>28</td>
</tr>
<tr>
<td>Surgery type, No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meniscectomy</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Meniscectomy and chondral debridement</td>
<td>25</td>
<td>18</td>
</tr>
<tr>
<td>Chondral debridement</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

**Abbreviation:** postop, postoperatively.
ing analyses, such that the postanesthesia care unit results included more patients than did the postdischarge results.

**In Hospital**

At no time point during in-hospital care did the study groups differ with respect to pain (VAS scores) or medication use (Table 2).

**Postdischarge**

In the 24-hour period following discharge from the hospital, the study groups did not differ with respect to pain or medication use (Table 3).

**Side Effects**

Side effects were infrequent, with only 5 patients across both groups reporting symptoms (Table 3). The upper bound of the 95% confidence interval for the pre- to postoperative differences in VAS scores between groups reached just 2 points at admission to the postanesthesia care unit, but for all other time points, the upper bound of the 95% confidence interval was 1.5 points or less. Consequently, 95% confidence exists that the difference between the groups with respect to postoperative pain was 2 points or less on the VAS in the in-hospital period and 1.5 points or less in the postdischarge period. Thus, the differences between the groups can be interpreted as clinically negligible with high confidence.

**DISCUSSION**

In the past few years, several articles have been published suggesting that intraarticular bupivacaine and lidocaine have a detrimental effect on hyaline cartilage.1-5 The goal of this study was to seek an alternative intra-articular medication that could substitute for the use of bupivacaine and lidocaine in the postoperative setting. The postoperative setting is more ideal for a substitute because it circumvents the need for immediate relief desired with office injections. Based on the current data, morphine can serve as an effective substitute for bupivacaine for postoperative analgesia for knee arthroscopy. Several medications have been studied in the past as alternatives for postoperative analgesia, including neostigmine, clonidine, morphine, and various anti-inflammatory agents. In particular, morphine is an opioid and acts on naturally occurring opioid receptors in the synovial lining of the knee.18 Morphine and bupivacaine have been compared in the past, with some studies indicating that bupivacaine is superior and others concluding that morphine is superior for postoperative pain control.3-5,12,14-16,18,19,22 In addition, despite that fact that many studies have compared morphine and bupivacaine, several studies have been confounded with variables such as dosing of administered medications, variable volumes of administration, variable surgical anesthetic protocols, variable use of tourniquets, use of postoperative drains, variety of procedures performed, and use of epinephrine, which render the data less useful for current clinical practice.8,9,12,14-16,18,19,22

In a randomized double-blind trial, Cepeda et al9 compared use of 10 mg of intra-articular morphine in 20 cc of volume, 20 cc of intra-articular .5% marcaine with epinephrine, and 10 mg of subcutaneous morphine with a 20-cc injection of saline. They used a tourniquet and kept it inflated for 5 minutes after medication administration. Intraoperative anesthesia included sodium pentothal and isoflurane or enflurane, as well as IV fentanyl. Various procedures were performed, including meniscectomy, lateral release, and meniscal repair. Average operative time was approximately 53 minutes. Using the VAS, assessment of postoperative narcotic use, and assessment of side effects, it was concluded that the intra-articular morphine gave statistically better relief at 6 and 24 hours with no increase in side effects, but it did not reduce the postoperative narcotic requirements.

Haynes et al14 performed a double-blind, placebo-controlled study comparing use of 1 mg of intra-articular morphine, .25% marcaine with epinephrine, .25% marcaine with epinephrine and morphine, and normal saline control. All medications were given at a volume of 40 mL. Each group comprised 10 patients, and, in addition to the intra-articular medication, each skin incision was infiltrated with 10 cc of .25% marcaine. Half of the surgical procedures were complete meniscectomies. It was concluded that the intra-articular morphine group had lower pain scores, but no statistical significance was shown. The morphine group also used less postoperative narcotic.14

Heard et al15 performed a prospective randomized, double-blind study comparing use of 20 cc of .03% morphine (6 mg), .25% bupivacaine, and normal saline. The

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**Table 2**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Morphine Group</th>
<th>Bupivacaine Group</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Mean VAS pain score</td>
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<td></td>
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<tr>
<td>Admission PACU</td>
<td>3.4±2.6</td>
<td>2.6±2.9</td>
<td>.217</td>
</tr>
<tr>
<td>Discharge PACU</td>
<td>3.0±1.6</td>
<td>2.6±2.1</td>
<td>.323</td>
</tr>
<tr>
<td>Admit PCU</td>
<td>3.9±1.9</td>
<td>3.3±2.3</td>
<td>.238</td>
</tr>
<tr>
<td>Discharge PCU</td>
<td>2.4±1.5</td>
<td>2.4±1.5</td>
<td>.875</td>
</tr>
<tr>
<td>Medication use, %b</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PACU</td>
<td>78.3</td>
<td>67.6</td>
<td>.418</td>
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<tr>
<td>PCU</td>
<td>69.6</td>
<td>61.8</td>
<td>.624</td>
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</table>

Abbreviations: PACU, postanesthesia care unit; PCU, progressive care unit; VAS, visual analog scale.

*Tested using t test and Mann-Whitney U test.

Percent of patients receiving pain medication and experiencing side effects, respectively; tested using chi-square test.
surgical procedures were not well delineated, and the postoperative pain medication protocols were not standardized. In addition, some patients received regional anesthesia (spinal), which affected the outcome. Both the morphine and the bupivacaine were administered with epinephrine. The authors found that bupivacaine provided good postoperative pain relief by several criteria, whereas the morphine only delayed the onset of first analgesic use compared with the control. 

Marchal et al\textsuperscript{10} compared the effects of intra-articular morphine and bupivacaine in high inflammatory and low inflammatory arthroscopic procedures. Based on the proposed mechanisms of action, they hypothesized that morphine would be more effective for the high inflammatory procedures and bupivacaine would be more effective for the low inflammatory procedures. They compared the use of 25 cc of .25% bupivacaine with epinephrine with 25 cc of 5 mg of morphine. They used a tourniquet in all cases and a suction drain in selected cases. All operative times were relatively long: the low inflammatory cases required an average of more than 50 minutes of operative time. The results indicated that bupivacaine resulted in lower VAS scores at 4 and 8 hours in the low inflammatory cases and morphine resulted in lower VAS scores at 24 hours in the high inflammatory group. No differences existed in postoperative narcotic consumption.\textsuperscript{18}

Ruwe et al\textsuperscript{22} performed a double-blind trial comparing morphine with bupivacaine. They used each drug separately, a combination of both, and a placebo control with normal saline. The highest dose of morphine used was 2 mg. They concluded that morphine alone had no effect on postoperative pain, use of supplemental anesthesia, or alteration in weight-bearing status. The combination of morphine and bupivacaine was not better than bupivacaine alone.\textsuperscript{22}

Follak and Ganzer\textsuperscript{12} performed a prospective randomized, double-blind study comparing use of 15 cc of .5% bupivacaine with 5 mg of morphine in a 15-cc volume. Each group comprised 80 patients and included several surgical procedures, including notchplasty, bone-patellar tendon-bone autograft, anterior cruciate ligament reconstruction, and meniscectomy. They placed suction drains in all patients and opened it to suction 15 minutes after administration of the medication. They found that bupivacaine was more effective than morphine for postoperative pain control at all time points.\textsuperscript{12}

De Andres et al\textsuperscript{9} compared use of 1 mg of morphine to .25% bupivacaine and a combination of both medications in a 20-cc volume. The study group comprised 103 patients undergoing meniscectomy. They also tracked the pH of the injected solutions to confirm that this was not a confounding variable. No difference existed among the groups for postoperative pain control.\textsuperscript{9}

McSwiney et al\textsuperscript{10} performed a randomized, double-blind study comparing use of a placebo, 5 mg of morphine, .25% bupivacaine, and 5 mg of morphine with .25% bupivacaine in a 25-cc volume. Each group comprised 10 patients. They found that the combination of morphine and bupivacaine was the most effective in reducing postoperative pain scores.\textsuperscript{19}

Richardson et al\textsuperscript{21} performed a prospective randomized trial comparing 5 mg intra-articular morphine, 1 mg of intra-articular morphine, and 5 mg of IV morphine in 48 patients after knee arthroscopy. They found that 5 mg of intra-articular morphine was most effective but did not reach statistical significance until later time points. They also assessed IV morphine levels 2 hours after an intra-articular injection and noted that the plasma level for a 5-mg intra-articular injection yielded a peripheral venous level of 3.5 ng/mL, which is lower than the 6.4 ng/mL noted 2 hours after an IV injection. In addition, they assessed the presence of nausea and

<table>
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<tr>
<th>Time, h</th>
<th>Morphine Group</th>
<th>Bupivacaine Group</th>
<th>P</th>
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<tbody>
<tr>
<td>4</td>
<td>3.0±2.3</td>
<td>2.8±2.0</td>
<td>.618</td>
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<td>8</td>
<td>2.7±1.8</td>
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<td>.376</td>
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<td>12</td>
<td>2.1±2.3</td>
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<td>16</td>
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<td>1.8±1.8</td>
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<td>20</td>
<td>1.5±1.9</td>
<td>1.8±2.3</td>
<td>.497</td>
</tr>
<tr>
<td>24</td>
<td>1.5±1.9</td>
<td>1.8±2.3</td>
<td>.608</td>
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<table>
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<tr>
<th>Medication use, %\textsuperscript{b}</th>
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<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
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<tbody>
<tr>
<td>Bupivacaine</td>
<td>67.6</td>
<td>58.8</td>
<td>64.7</td>
<td>44.1</td>
<td>52.9</td>
<td>52.9</td>
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<tr>
<td>Morphine</td>
<td>71.7</td>
<td>58.8</td>
<td>64.7</td>
<td>44.1</td>
<td>52.9</td>
<td>52.9</td>
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<tr>
<td>P</td>
<td>.882</td>
<td>.333</td>
<td>.999</td>
<td>.627</td>
<td>.190</td>
<td>.901</td>
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<table>
<thead>
<tr>
<th>Side effects, %\textsuperscript{b}</th>
<th>4 (nausea, itching)</th>
<th>8 (nausea)</th>
<th>12 (nausea)</th>
<th>16</th>
<th>20</th>
<th>24 (dry mouth)</th>
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<tbody>
<tr>
<td>Bupivacaine</td>
<td>10.6</td>
<td>4.3</td>
<td>2.1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Morphine</td>
<td>10.6</td>
<td>4.3</td>
<td>2.1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>P</td>
<td>.068</td>
<td>.326</td>
<td>.573</td>
<td>NA</td>
<td>NA</td>
<td>.427</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not available; VAS, visual analog scale.
\textsuperscript{a}Tested using t tests and Mann-Whitney U test.
\textsuperscript{b}Percent of patients receiving pain medication and experiencing side effects, respectively; tested using chi-square test.
noted no correlation between nausea and the plasma levels of morphine. The incidence of nausea was low and not statistically different between the low- and high-dose morphine groups.21

Jaureguito et al16 compared 4 mg of morphine, 25% bupivacaine, and 9% saline using the VAS and measuring supplemental pain medication at several time points until 24-hours postoperatively. They found that the morphine was as effective as the bupivacaine at early time points and better at later time points. They enrolled 14 patients in morphine and bupivacaine groups and 12 in the saline group. In addition, all procedures were performed while the patients were under local anesthesia, so all patients, regardless of group, received 30 mL of intra-articular lidocaine and epinephrine and 10 mL in each portal preoperatively in addition to the postoperative injection.16

The current study controlled for many of the confounding factors in prior studies, including clinically low doses of morphine, use of epinephrine, use of suction drains, use of tourniquets, types of cases enrolled, and nonstandardized anesthesia protocols. The current authors implemented a rigorous and consistent intra- and postoperative anesthesia and analgesia protocol; controlled the types of cases included; and excluded other confounding variables, such as the use of epinephrine, use of tourniquets, use of postoperative drains, low doses of medication, and high volumes of injected fluid.

This study has limitations. The authors were unable to gather data for all patients because of lack of compliance and a lack of understanding how to follow the protocol and fill out the VAS sheets. The authors were concerned about recall bias if the patients did not immediately fill out the postdischarge questionnaires, so they were not asked to complete them later if they did not do so immediately. The authors called the patients within 24 hours of discharge to check on them, but that did not always stimulate compliance. In addition, more than the necessary number of patients were recruited, but 1 group randomly had more patients than the other, and the attrition rate exceeded what was estimated.

The study included a sufficient number of patients based on the preoperative power analysis to make conclusions on the in-hospital data, but the postdischarge period included only 28 patients in the bupivacaine group and not the 34 needed for a 2-point VAS difference. However, the upper bound of the 95% confidence interval for the pre- to postoperative differences in VAS scores between groups reached 2 points at admission to postanesthesia care unit, but for all other time points, the upper bound of the 95% confidence interval was 1.5 points or less. Consequently, the 95% confidence interval indicated that the difference between the groups with respect to postoperative pain was 2 points or less on the VAS in the in-hospital period and 1.5 points or less in the postdischarge period. Thus, the differences between the groups can be interpreted as clinically negligible with high confidence.

The study group was not truly homogenous, with 9 patients undergoing chondral debridement alone, 30 undergoing an isolated meniscectomy, and 43 undergoing both. Many of the chondral debridements were patellar and were minimal interventions that could have been left alone, but that would have been ethically problematic had the patient not seen benefit from the surgery. In addition, some would argue that pain after a meniscectomy may not be as severe as after other procedures, but the authors wanted to test a group of patients with a common surgery before considering it on other more complex procedures. Furthermore, the authors did not differentiate time spent in the postanesthesia care unit and progressive care unit postoperatively, but it would presumably only be increased in the few patients with side effects. Moreover, the authors did not quantify differences in articular cartilage damage and severity of osteoarthritis; the groups were selected by the same exclusion criteria, and 43 of 73 meniscectomy procedures involved chondral debridement, suggesting a low level of early osteoarthritis in many patients consistent with an average age of 50 years. As previously mentioned, the surgeon performed a minimal debridement of the chondral surfaces, which may not add significantly to the pain management of the procedure but may be important in the potential surgical benefit and the potential detrimental effect of bupivacaine.

The authors acknowledge the potential criticisms of this study that, as in other studies, may decrease the overall value of the study; however, the study adds important evidence that supports an alternative drug regimen to intra-articular bupivacaine. Despite these potential criticisms, the authors collected sufficient data to compute 95% confidence intervals, which supports the conclusion of a clinically negligible difference in efficacy of injection type. This is a methodologically sound study that used a sufficient dose of morphine to demonstrate that morphine is as effective as bupivacaine for postoperative pain relief for knee arthroscopy with meniscectomy with or without chondral debridement. This study is timely because it provides an alternative postoperative analgesia regimen that is effective and avoids the potential detrimental effects of intra-articular bupivacaine.

**CONCLUSION**

Ten milligrams of intra-articular morphine is as effective as 10 cc of 0.5% bupivacaine for postoperative pain control for partial meniscectomy and chondral debridement of the knee. It minimally increases the side effects initially, and it circumvents the issue of chondral toxicity of bupivacaine.

**REFERENCES**


