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Postarthroscopy Analgesia with Intraarticular Bupivacaine/Morphine

A Randomized Clinical Trial

Gregory C. Allen, M.D., FRCPC,* Marc A. St. Amand, M.D.,† Anne C. P. Lui, M.D., FRCPC,‡
Donald H. Johnson, M.D., FRCSC,§ M. Patrice Lindsay, B.Sc.N.‖

Background: **Postarthroscopy analgesia has been provided with intraarticular bupivacaine, but the duration of analgesia may be only a few hours. More recently, longer-lasting analgesia has been achieved using intraarticular morphine, although the onset of analgesia may be delayed. The combination of intraarticular morphine and bupivacaine has been suggested as an ideal analgesic after knee arthroscopy.**

Methods: **One hundred and twenty ASA Physical Status 1–2 outpatients, age 18–60 yr, having knee arthroscopy, were randomized into one of four treatment groups. Exclusion criteria included relevant drug allergy, extensive debridement or synovectomy, arthrotomy, postoperative intraarticular drainage, tracheal intubation, and patient refusal. All patients received general anesthesia with intravenous fentanyl, propofol, N_2O, O_2, and isoflurane. At the end of surgery, before tourniquet release, the following were injected intraarticularly through the arthroscope: group 1, 0.25% bupivacaine; group 2, 1 mg morphine in saline; group 3, 2 mg morphine in saline; and group 4, 1 mg morphine in 0.25% bupivacaine. The volume injected was 30 ml, and all solutions contained 1:200,000 epinephrine. Postoperative analgesia was provided with intravenous fentanyl and/or oral acetaminophen/codeine, and was recorded for 24 h. Visual analog pain scale (VAPS) scores and the McGill Pain Questionnaire (MPQ) were performed hourly from 1–6 h, and at 24 h postoperatively.**

Results: **Visual analog pain scale and MPQ scores were lowest in groups 1 and 4 at 1–6 h, but at 24 h, VAPS scores were lowest in groups 2, 3, and 4. Analgesic requirements were lower for the first 12 h in groups 1 and 4, but no difference was seen between groups over the 24-h study period. No adverse effects were noted.**

Conclusions: **Morphine, 1 mg intraarticular, in 30 ml 0.25% bupivacaine, with 1:200,000 epinephrine, may provide superior postoperative analgesia for up to 24 h *versus* bupivacaine or morphine alone. (Key words: Analgesics, opioid: morphine. Anesthetic techniques: intraarticular. Anesthetics, local: bupivacaine. Pain: postoperative. Surgery: arthroscopy.)**

SATISFACTORY analgesia after arthroscopic knee surgery can be provided with intraarticular bupivacaine,[1] but relief may last for only a few hours.[2] In contrast, intraarticular morphine has been shown to produce significant, but delayed, postoperative analgesia after arthroscopic knee surgery.[3] Peripheral opioid receptors have been implicated in mediating this effect.[4] However, two subsequent studies have questioned the efficacy of intraarticular morphine,[5,6] after observing no difference in pain scores in patients who received either intraarticular morphine or saline placebo.

If intraarticular morphine does have an analgesic effect, then the combination of intraarticular morphine and bupivacaine should be ideal for postoperative analgesia. Because the time of onset and duration of action of these two agents appear to complement each other, analgesia should be immediate and long lasting. Khoury *et al.* concluded this after comparing intraarticular morphine, bupivacaine, or a combination of the two in 33 patients.[7] Pain scores and postoperative analgesic consumption were lowest in patients who received both agents.

Given the conflicting evidence for an analgesic effect of intraarticular morphine,[4] and the relatively small number of patients studied, we performed a larger,

* Assistant Professor, Department of Anesthesia, College of Medicine, The Pennsylvania State University.

† Resident, Department of Anaesthesia, University of Ottawa, Ottawa.

‡ Clinical Lecturer, Department of Anaesthesia, University of Ottawa; Staff Anaesthetist, Ottawa Civic Hospital.

§ Assistant Professor, Division of Orthopedic Surgery, University of Ottawa; Attending Surgeon, Ottawa Civic Hospital.

‖ Research Nurse, Department of Anaesthesia, Ottawa Civic Hospital.

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Address reprint requests to Dr. Allen: Department of Anesthesia, College of Medicine, The Pennsylvania State University, P.O. Box 850, Hershey, Pennsylvania 17033.

randomized clinical trial. We examined the analgesic effect of intraarticular morphine, compared with intraarticular bupivacaine, and a combination of intraarticular morphine and bupivacaine, after arthroscopic knee surgery. In addition, two different dosages of intraarticular morphine were compared, to determine if the larger dosage would produce more effective analgesia.

Materials and Methods

Following institutional approval, patients gave informed consent to participate in a double-blind, randomized clinical trial. All were ASA Physical Status 1–2 outpatients, ages 18–60 yr, requiring arthroscopic knee surgery. Procedures included diagnostic arthroscopy, meniscectomy, and removal of loose body. Exclusion criteria included relevant drug allergy, need for surgical debridement or synovectomy (because of possible increased vascular absorption of study drugs[8]), need for arthrotomy or postoperative intraarticular drainage, need for tracheal intubation, or patient refusal.

Patients received general anesthesia, in adherence with the study protocol. Preoperative sedation, if required, consisted of 1–3 mg intravenous midazolam. Anesthesia was induced with 1–2 μg/kg intravenous fentanyl and 1–2 mg/kg intravenous propofol, and maintained with 70% nitrous oxide in oxygen and 1–2% inspired isoflurane. Patients breathed spontaneously *via* facemask or laryngeal mask airway for the duration of the procedure. All procedures were performed by the same surgeon (DHJ) using a standard technique.

Using a random number table, each patient was randomized to one of four groups: group 1 received 0.25% intraarticular bupivacaine, group 2 received 1 mg intraarticular morphine in normal saline, group 3 received 2 mg intraarticular morphine in normal saline, and group 4 received 1 mg intraarticular morphine in 0.25% bupivacaine. The volume of injection was standardized at 30 ml, and all solutions contained 1:200,000 epinephrine. The study solution, supplied in a coded syringe, was injected into the knee joint at the end of surgery, 3–5 min before tourniquet release.

During recovery, patients received 0.05 mg intravenous fentanyl and/or oral Tylenol #3 (acetaminophen 300 mg/codeine 30 mg, McNeil Pharmaceuticals, Don Mills, Ontario) for complaints of inadequate analgesia. Patients were discharged from the hospital with a prescription for Tylenol #3 (1–2 tablets Q4-6H, as required), and were asked to record their analgesic intake. Analgesics required in the recovery room, and the time to hospital discharge were recorded. The presence of nausea, vomiting, pruritus, or somnolence were noted for each patient.[3]

Analgesia was assessed using a 100-mm visual analog pain scale (VAPS),[9–11] a 0–100 Numeric Rating Scale (NRS),[12] and the McGill Pain Questionnaire[9,12,13] hourly for 6 h, and at 24 h postoperatively. Pain measures were explained to each patient preoperatively by a blinded observer, and all pain measures were performed immediately after the patient actively flexed the operated knee to 90°. When patients were discharged from the hospital, they were asked to complete their pain measures at the predetermined times and record their analgesic intake. Each patient was interviewed by telephone 24 h postoperatively, and the patient-recorded data were returned by stamped, addressed envelopes.

Data analysis was performed by repeated measures ANOVA, Neuman-Keuls *post hoc* tests, chi-squared tests, and Kruskall-Wallis tests. We assumed that intraarticular morphine would produce a 50% reduction in VAPS scores at 3–6 h,[3] compared with bupivacaine. Using an α of 0.05 and a power of 0.8, a sample size calculation determined that 232 patients were required to avoid a Type II error. Block randomization was used, with a block size of 60 patients. Data from each consecutive block was analyzed, and if the 50% reduction in VAPS scores was observed, the trial was terminated. Otherwise, the trial would continue until 240 patients had been studied. Statistical significance was determined at the level of $p < 0.05$.

Results

We obtained consent from 144 consecutive patients to participate in this study. There were 24 patients who were subsequently excluded for the following reasons: extensive debridement (10), subsequent request for spinal anesthesia (5), need for tracheal intubation (3), subsequent patient withdrawal (3), relevant drug allergy (2), no surgery performed (1). The trial was stopped after 120 patients when the predetermined primary outcome measure (50% reduction of VAPS scores at 3–6 h) had been achieved. Data were collected on the 120 patients during their outpatient admission. Fully completed pain measures (0–24 h) were obtained for 106 (88%) patients. There were no differences between groups in age, gender, or body weight (table 1). The mean dosages of fentanyl and midazolam

Table 1. Demographic and Intraoperative Data

Group	Age (yr)	Gender (M/F)	Body Weight (kg)	Fentanyl (μg)	Midazolam (mg)	Surgical Time (min)	No. of Meniscectomies
1	32.3 ± 8.8	24/6	78.9 ± 13.6	103.2 ± 41.4	1.0 ± 0.86	25.6 ± 9.3	26/30
2	35.1 ± 9.7	24/6	79.1 ± 16.4	105.2 ± 35.5	0.75 ± 0.92	29.0 ± 12.0	22/30
3	31.4 ± 9.3	23/7	79.5 ± 10.8	111.7 ± 40.3	0.87 ± 0.84	29.6 ± 11.1	24/30
4	38.6 ± 13.7	22/8	82.5 ± 14.4	115.5 ± 16.1	0.53 ± 0.81	33.1 ± 16.1	20/30

Values are mean ± SD, where applicable.

There was no significant difference between groups.

given intraoperatively, the types of surgical procedures, and the duration of surgery were also similar.

Over the 24-h study period, the lowest VAPS scores were seen in group 4 (fig. 1). Visual analog pain scale scores were similar in groups 1 and 4 for the first 6 h after surgery, and were significantly less than those for groups 2 and 3. Group 3 had significantly greater VAPS scores than group 2 for 1–6 h, despite receiving the larger dose of intraarticular morphine. At 24 h, group 1 had higher VAPS scores than groups 2, 3, or 4, whose pain scores were similar (fig. 1). Pain scores measured by NRS were similar to those of the VAPS (results not shown). The MPQ was analyzed using the Pain Rating Index (PRI) and the total number of words (TNW).[13] The PRI and TNW results were similar, and only the PRI results are presented (fig. 2). The MPQ results were consistent with VAPS scores at 1–6 h postoperatively (fig. 2); however, all four groups had similar MPQ scores at 24 h.

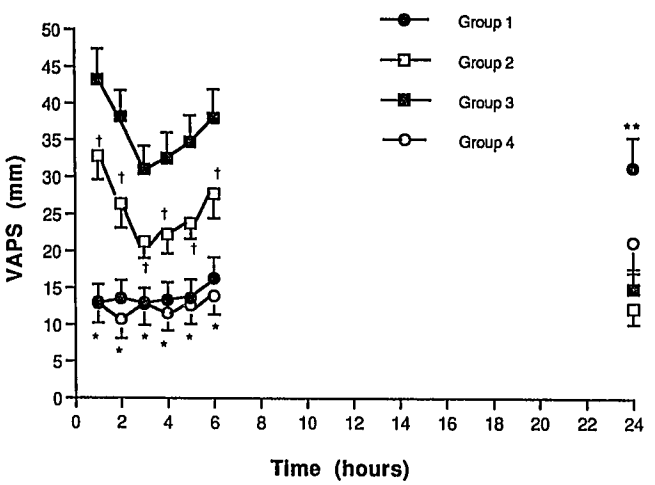

Fig. 1. Visual analog pain scale (VAPS) scores (mean ± SEM) *versus* time (h). *$P < 0.05$ for groups 1 and 4 *versus* 2 and 3 at 1–6 h; †$P < 0.05$ for group 2 *versus* 3 at 1–6 h; **$P < 0.05$ for group 1 *versus* 2, 3, and 4 at 24 h.

Patients in groups 1 and 4 required less supplemental analgesia in hospital (table 2) and for the first 12 h after discharge (table 3). The time to first analgesic after discharge was also longer (table 3). Significantly more patients in group 3 took analgesics during the first 12 h after hospital discharge. However, in patients who used analgesics, there was no difference in total analgesic intake over the first 24 h (table 3).

No adverse side effects were noted with the administration of intraarticular morphine. There was no difference between groups in the incidence of nausea and vomiting (table 4). One patient, with a history of postoperative emesis, had severe nausea and vomiting; he received intraarticular bupivacaine alone (group 1). There were no cases of pruritus or somnolence. The time until patients were fit for hospital discharge was similar between groups.

Discussion

In this clinical trial, patients who received 1 mg intraarticular morphine in combination with 0.25% bupivacaine had less pain during the first 24 h after knee arthroscopy. This supports Khoury *et al.*,[7] who studied 33 patients undergoing knee arthroscopy, comparing intraarticular morphine, bupivacaine, and the combination of the two. They concluded that the combination of 1 mg intraarticular morphine in 0.25% plain bupivacaine provided superior analgesia. Visual analog pain scale scores and analgesic requirements remained lower through the second postoperative day in the group receiving morphine/bupivacaine.

Management of acute pain after surgery is no longer a problem restricted to the postoperative period. Although "preemptive" analgesia has been advocated,[14] it is not known whether such strategies must precede noxious stimuli to attenuate postoperative pain.[15] Local anesthetics can block sensory afferents before surgery,[16] but peripheral opiate receptors are activated only in

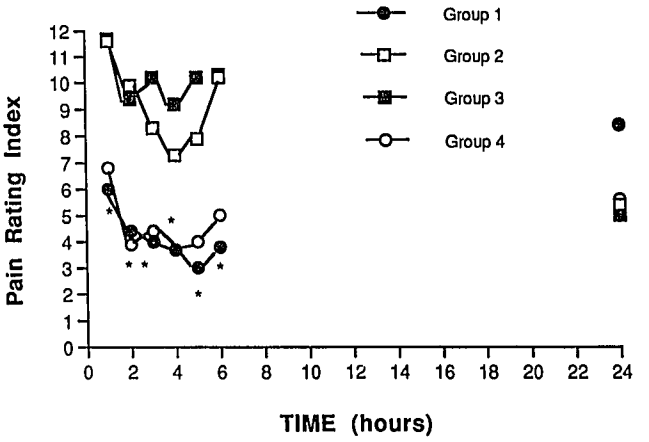

Fig. 2. Pain Rating Index (PRI) from the McGill Pain Questionnaire *versus* time (h). *$P < 0.05$ for groups 1 and 4 *versus* 2 and 3 at 1–6 h.

the presence of tissue inflammation.[4] Lawrence *et al.* have identified opioid binding sites in synovial tissue,[17] indicating that the analgesia is locally mediated.[4]

It seems unlikely that intraarticular morphine acts systemically, because one would not expect such profound analgesia from 1 mg morphine. Joshi *et al.* measured plasma morphine concentrations for 4 h in ten patients who each received 5 mg intraarticular morphine.[18] Plasma levels of morphine were considered subanalgesic in eight of ten patients, but these patients reported less pain for up to 24 h. This favors a peripheral opiate action as the mechanism of such prolonged analgesia.[3]

In our study, analgesia did not appear to improve with a larger dose of morphine. Although Stein *et al.* observed lower pain scores with 1 *versus* 0.5 mg intraarticular morphine,[3] we found that patients who received 2 mg intraarticular morphine had higher pain scores for the first 6 h after surgery. Dose dependence provides evidence of an opioid receptor-mediated effect.[4] The increased pain scores observed after 2 mg intraarticular morphine were unexpected, and indicate a paradoxical response. However, Joshi *et al.* used 5 mg intraarticular morphine *versus* saline placebo, and observed effective analgesia for 12–24 h after knee arthroscopy[18] and after anterior cruciate ligament repair.[19]

In contrast, studies by Raja *et al.*,[6] using 3 mg intraarticular morphine, and by Heard *et al.*,[5] using 6 mg intraarticular morphine, failed to observe an analgesic effect. Raja *et al.*[6] used epidural anesthesia, which may have reduced postoperative pain by attenuating spinal cord hyperexcitability.[14] The study protocol of Heard *et al.* was not standardized: patients received regional or general anesthesia in a nonrandomized fashion, some patients inadvertently received fentanyl, and a variety of postoperative analgesics were used.[5] The "negative" results in both studies may have been caused by an inadequate numbers of subjects (Type II error).[20]

Table 2. Number of Patients Who Required Postoperative Analgesia in Hospital

Group	None	Fentanyl	Tylenol 3
1	22	2†	6‡
2	13	13	13
3	4*	21	19
4	20	2†	8‡

N = 30 for all groups; some patients received both fentanyl and Tylenol 3 while in the hospital.

* Group 3 *versus* 1, 2, 4; $P = 0.001$.

† Group 1, 4 *versus* 2, 3; $P = 0.0001$.

‡ Group 1, 4 *versus* 2, 3; $P = 0.003$.

Table 3. Time to First Analgesic, Number of Patients Using Analgesics after Hospital Discharge, and 24-h Total Analgesic Intake for Patients Who Used Them

Group	Time (h)	No. of Patients 0–6 h	6–12 h	12–24 h	24-h Intake (no. of tablets)
1	7.0 ± 6.3*	2/30	13/30§	12/30	2.5 ± 1.9 (1–8)
2	3.0 ± 3.9	6/30	19/30	13/30	3.2 ± 1.8 (1–9)
3	1.5 ± 2.9†	15/30‡	24/30	17/30	3.6 ± 1.9 (1–8)
4	4.6 ± 4.5	8/30	14/30§	13/30	3.2 ± 2.1 (1–8)

Values are mean ± SD; values in parentheses are ranges.

* Group 1 *versus* 2; $P = 0.001$.

† Group 3 *versus* 1, 4; $P = 0.014$.

‡ Group 3 *versus* 1, 2, 4; $P = 0.001$.

§ Group 1, 4 *versus* 2, 3; $P = 0.014$.

Table 4. Time to Hospital Discharge and Frequency of Adverse Events during Recovery

Group	Discharge Time (min)	Nausea	Vomiting	Somnolence/Pruritis
1	121 ± 47	6/30	1/30	0/30
2	127 ± 55	6/30	1/30	0/30
3	134 ± 52	7/30	1/30	0/30
4	114 ± 32	4/30	1/30	0/30

There was no significant difference between groups.

The volume injected into the joint space may be important to intraarticular opiate action.[5,18] Heard *et al.* and Raja *et al.* used a 20-ml volume, without observing a significant analgesic effect.[5,6] In our study and those of Stein *et al.* and Joshi *et al.*, larger volumes were injected (30, 40, and 25 ml, respectively),[3,18,19] and at least some analgesic effect was seen. However, Khoury *et al.* reported that a 20-ml volume produced satisfactory analgesia.[7]

In this study, epinephrine was added to all intraarticular solutions, to avoid a possible confounding variable.[5] Its use has also been recommended to prevent local anesthetic toxicity.[21] In previous studies of intraarticular bupivacaine alone, it was seldom stated whether a vasoconstrictor was used, and this may account for its variable efficacy. In our study, patients who received 1 mg intraarticular morphine with epinephrine (groups 2 and 4) reported VAPS scores similar to patients of Stein *et al.* and Khoury *et al.* who did not receive intraarticular epinephrine.[3,7] We suggest that the addition of epinephrine will not reduce the analgesic effect of intraarticular morphine and/or bupivacaine, and may prolong the duration of analgesia.

Another potentially confounding variable was the use of outpatients to study intraarticular analgesia. In two studies that support the efficacy of intraarticular morphine, patients were admitted to the hospital overnight and received parenteral narcotics for postoperative pain.[3,18] We studied outpatients, which may account for the increased pain scores 3–6 h after surgery. Once our patients left the hospital, they reported varying levels of activity. Other measures of analgesia, such as sleep disturbance, have not been addressed.

Our primary outcome assessment was a reduction in VAPS scores. We observed significantly lower VAPS scores at 24 h in patients who received intraarticular morphine (groups 2–4). The differences in VAPS scores were not caused by increased analgesic intake, because all four groups used similar amounts. We do not know why patients in group 1 did not increase their analgesic intake in response to increased perception of pain. Patients were told to take up to 12 tablets/24 h, yet no patient took more than 9 tablets. Some patients reported taking analgesics before retiring at night, while pain free, to avoid possibly awakening in pain during the night. Given the variability in patient behavior, 24 h of total analgesic intake may not be a reliable measure of intraarticular analgesic efficacy, at least in outpatients.

The VAPS and NRS scores were similar within groups over time, and performing both was unnecessary. The MPQ is a multidimensional scale used primarily to assess chronic pain,[13] but it has also been applied to acute pain. The Pain Rating Index (PRI) is the sum of rank values for all of the words chosen on the MPQ. The Total Number of Words (TNW) is the sum of words chosen by the patient. Patients may not necessarily choose words from all 20 categories in the MPQ. The PRI and TNW results were similar to those of the VAPS except at 24 h, when no difference was seen. This may have been because the MPQ was not our primary outcome assessment, and an insufficient number of patients were studied. Our results were similar to those of Stein *et al.*,[3] in which PRI scores were significantly lower at 3–6 h in patients who received 1 mg intraarticular morphine *versus* saline, but no difference was seen at 24 h. Reading has reported correlations of 0.10–0.35 between VAPS and MPQ scores,[22] which indicates that the MPQ may not be ideal for assessing some forms of acute pain.[23]

Our patients were asked to flex their knee to 90° before scoring their pain. By stressing the joint, the degree of pain and adequacy of analgesia were better assessed. Such testing has been recommended for the assessment of postoperative pain,[12] especially when assessing outpatients for discharge home.[24]

In summary, 1 mg intraarticular morphine in 30 ml 0.25% bupivacaine with 1:200,000 epinephrine provided superior analgesia for up to 24 h after knee arthroscopy, compared with bupivacaine or morphine alone. Intraarticular morphine, 2 mg, alone led to higher pain scores *versus* 1 mg. We now routinely use the combination of intraarticular morphine and bupivacaine to provide analgesia after knee arthroscopy.

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