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Intraarticular Morphine, Bupivacaine, and Morphine/Bupivacaine for Pain Control after Knee Videoarthroscopy

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Evidence has accumulated that opioids can produce potent antinociceptive effects by interacting with opioid receptors in peripheral tissues. This study sought to compare the effects of morphine with those of bupivacaine administered intraarticularly upon pain following arthroscopic knee surgery. In a double-blind, randomized manner, 33 patients received either morphine (1 mg in 20 ml NaCl; n = 11), bupivacaine (20 ml, 0.25%; n = 11), or a combination of the two (n = 11) intraarticularly at the completion of surgery. After 1, 2, 3, and 4 h and at the end of the 1st and 2nd postoperative days, pain was assessed by a visual analogue scale, and supplemental analgesic requirements were recorded. Pain scores were significantly greater in the morphine group than in the other two groups at 1 h. There were no significant differences at 2 and 3 h. From 4 h until the end of the study period, pain scores were significantly greater in the bupivacaine group than in the other two groups. Analgesic requirements were significantly greater in the morphine group than in the other groups at 1 h but were significantly greater in the bupivacaine group than in the other groups throughout the remainder of the study period. We conclude that intraarticular morphine produces an analgesic effect of delayed onset but of remarkably long duration. The combination of these two drugs results in satisfactory analgesia throughout the entire observation period. (Key words: Analgesics, opioid: morphine. Anesthetics, local: bupivacaine. Anesthetic techniques: intraarticular. Pain: postoperative.)

OPIOID ANALGESIA has been associated with activation of opioid receptors within the central nervous system. Evidence has also accumulated that exogenous[1–3] as well as endogenous[4,5] opioids can produce pronounced antinociceptive effects by interacting with opioid receptors in peripheral tissues. We have been able to differentiate the types of opioid receptors involved[6] and to demonstrate such receptors on peripheral terminals of primary afferent neurons functionally[7] and *in situ*.[5] Furthermore, we have shown that peripherally administered opioids can elicit significant analgesic effects in humans.[8,9] Thus, low doses of intraarticular morphine, injected at the completion of arthroscopic knee surgery, can produce relatively long-lasting postoperative analgesia apparently *via* activation of local opioid receptors in the knee joint.[9]

Postoperative analgesia after arthroscopy has also been examined after the intraarticular administration of conventional local anesthetics.[10,11] So far, however, the results are equivocal. Thus, in patients receiving intraarticular bupivacaine, Henderson *et al.*[10] found no effect, whereas Chirwa *et al.*[11] found significantly reduced pain reports and supplemental analgesic use compared to controls.

The present study was designed 1) to examine the analgesic effect of intraarticular administration of a small dose of morphine upon postoperative pain in patients who had undergone arthroscopic knee surgery; 2) to compare the effect to that produced by a conventional local anesthetic, bupivacaine; and 3) to examine the effect of a combination of morphine and bupivacaine.

Materials and Methods

PATIENTS

The project was institutionally approved, and informed consent was obtained from each patient before surgery. Thirty-three outpatients undergoing arthroscopic knee surgery were studied. Surgical procedures included diagnostic tissue excisions, partial or total meniscectomies, and lateral release, with approximately equal representation among the groups. The criteria for exclusion from the study were ASA physical status rating of 3 and greater[12] and the requirement for postoperative intraarticular drainage. All patients received meperidine (1 mg/kg intramuscularly) and midazolam (0.03 mg/kg intramuscularly) 1 h before surgery. Anesthesia was induced with thiopental (4 mg/kg). Succinylcholine (1 mg/kg) was administered to facilitate tracheal intubation, after which anesthesia was maintained with O_2/N_2O and isoflurane (0.8–2.0%).

EXPERIMENTAL DESIGN

At the conclusion of surgery but before the arthroscope was removed, patients received one of the following so-

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lutions intraarticularly in a double-blind, randomized manner: 1 mg morphine-sulfate in 20 ml NaCl (n = 11), 20 ml 0.25% bupivacaine (n = 11), or 1 mg morphine sulfate in 20 ml 0.25% bupivacaine (n = 11). These doses were chosen based on previous animal and human studies.[6,8,9,11] Thereafter, general anesthesia was terminated. Since previous studies had shown that both intraarticular morphine and bupivacaine were more effective than saline,[8,9,11,13] we did not use such a control group, for ethical considerations.

Pain Assessment

Postoperative pain was assessed using a 10-cm visual analogue scale (VAS)[14] ranging from "no pain" to "unbearable pain." Scores were taken at 1, 2, 3, and 4 h after drug injection and at the end of the 1st and 2nd postoperative days, respectively. Supplemental analgesic medication was available upon request and was recorded at the above intervals. In the recovery room, fentanyl was given in increments of 0.05 mg and titrated to the patient's subjective level of comfort. Upon discharge from the hospital, the patients were instructed to use 1 or 2 codeine tablets every 3 h when needed, and were given a sheet of paper that had two VAS and a space for analgesics. They were asked to rate their pain intensity over the preceding 24 h and at the end of each postoperative day on the VAS and to record their analgesic usage at the same time. These sheets were then mailed back to the hospital by about 70% of the patients in each group.

Data Analysis

Demographic data were analyzed by analysis of variance (ANOVA).[15] To score the VAS, the distance (in millimeters) from the "no pain" end to the mark provided by the patient was measured. To determine supplemental analgesic requirements, meperidine doses were converted into codeine equivalents based on an equianalgesic ratio of 1:1.6.[16] Each patient's total consumption during their stay in the recovery room (1st h), in the outpatient department (2nd–4th h), and at home (1st and 2nd postoperative days) was calculated. Comparisons of pain scores between groups were made using the Kruskal-Wallis test and Dunn's procedure for *post hoc* evaluation. Comparisons of analgesic consumption between groups were made using an ANOVA and Fisher's least significant difference (LSD) procedure for *post hoc* testing.[15] A P value ≤ 0.05 was considered significant.

Table 1. Demographic Data

	Age (yr)	Weight (kg)	Duration of Surgery (min)
Morphine (n = 11)	44.0 ± 9.5	76.2 ± 2.7	67 ± 12
Bupivacaine (n = 11)	45.2 ± 8.0	74.3 ± 3.6	59 ± 7
Morphine + bupivacaine (n= 11)	44.9 ± 6.5	73.1 ± 2.2	61 ± 8

Means ± SEM are given.

Results

There were no significant differences (ANOVA) in patient demographics (table 1) and preoperative pain scores (average 12.4 ± 4 mm).

VAS scores were not different between groups up to 3 h postoperatively ($P > 0.05$, Dunn's test) except for the 1st h, when the morphine group displayed significantly greater values than the other two groups ($P < 0.006$, Dunn's test). From the 4th postoperative hour until the end of the study period (2nd postoperative day), pain scores were significantly greater in the bupivacaine group than in the other two groups ($P < 0.05$, Dunn's test) (table 2).

Supplemental analgesic consumption was significantly greater in the bupivacaine group than in the other two groups throughout the study period ($P < 0.05$, LSD test) except for the 1st h, during which time the morphine group required significantly more than the other two groups ($P < 0.001$, LSD test) (table 3).

Discussion

In patients who have undergone arthroscopic knee surgery, intraarticular morphine produces more pronounced analgesia than intraarticular bupivacaine between the 4th h and the end of the 2nd postoperative day, whereas bupivacaine is a superior analgesic during the 1st h postinjection. The combination of both substances produces satisfactory analgesia throughout the entire study period.

The analgesic efficacy of these treatments is documented by a direct subjective measure of pain intensity, the VAS,[14,17] and an indirect indicator, supplemental analgesic requirements. Both measures appear to correlate well, in that during the 1st h both VAS scores and analgesic requirements were significantly greater in the group receiving morphine alone than in the other two groups, and between the 4th h and the end of the study period, both measures were greater in the group receiving bupivacaine alone than in the other two groups. Despite the larger amounts of requested additional analgesics, the respective differences in reported VAS scores remain quite distinct. These differences might have been even greater in the absence of additional medication, which, however, was impossible to withhold for obvious ethical reasons.

TABLE 2. Visual Analogue Scores

Time	1 h	2 h	3 h	4 h	1 day	2 days
Morphine (G1)	56.0 ± 10 24.15	28.3 ± 11 17.33	22.8 ± 7 12.33	13.9 ± 7 14.66	18.6 ± 6 12.72	13.9 ± 5 13.67
Bupivacaine (G2)	22.3 ± 9 12.18	26.5 ± 11 15.30	22.5 ± 6 16.95	32.8 ± 9 20.40	36.8 ± 7 21.23	28.6 ± 6 21.55
Morphine + bupivacaine	20.0 ± 4 13.86	14.3 ± 6 14.18	20.6 ± 5 16.77	8.6 ± 4 11.72	20.2 ± 3 13.46	13.0 ± 4 12.36
F value	10.07	0.74	1.74	5.71	5.76	6.67
P value	0.006	NS	NS	0.05	0.05	0.04
Post hoc Comparison	G1 > G2 G1 > G3			G2 > G1 G2 > G3	G2 > G1 G2 > G3	G2 > G1 G2 > G3

Means ± SEM (millimeters) and mean ranks are given. Data were analyzed by Kruskal-Wallis' and Dunn's procedures. NS = difference not significant.

The present data suggest that intraarticular bupivacaine produces an immediate analgesic effect of relatively short duration, while morphine produces a much longer-lasting effect but with a delayed onset. These characteristics agree with previous reports examining the intraarticular administration of bupivacaine,[10,11,18] or morphine.[8,9,18]

To discuss these time courses of action, one has to consider several aspects. First, the question arises as to the site of action of these drugs. It is generally accepted that local anesthetics exert their effects through an action upon peripheral nerves, and the duration of action of bupivacaine observed here is entirely consistent with previous studies.[11,13,19] In the case of opioids, however, such effects have been demonstrated only recently. Thus, low doses of peripherally administered opioids can produce potent antinociceptive effects mediated by peripheral opioid receptors in inflamed tissue of the rat.[3,6,20] Moreover, in humans, low doses of intraarticular morphine can significantly inhibit postoperative pain by an activation of peripheral opioid receptors within the joint.[9] Similar to the spinal application of opioids, the duration of analgesia after intraarticular morphine appears to be considerably longer than after systemic administration.[21] The remote possibility of a central action of this small dose of morphine, although not examined here, has been excluded in a previous study.[9] Other possible explanations are morphine's low lipid solubility[21] and its slow rate of absorption into the circulation resulting therefrom, or a relatively low blood flow to the articular area. In contrast, the relatively high lipophilicity of bupivacaine[19] could account for its faster uptake into the circulation and consequent removal from the joint. On the other hand, if one assumes sensory nerves to be the common site of action of these drugs (see below), these physicochemical characteristics could explain morphine's delayed and bupivacaine's immediate onset of action.

Second, the mechanisms of action of these drugs have to be taken into account. Local anesthetics are thought to produce their effects through inhibition of the generation and/or propagation of action potentials at the neuronal membrane and a resulting blockade of afferent nociceptive barrage.[19] In the case of opioids, two different peripheral mechanisms may result in a decreased nociception. On the one hand, morphine may diminish local posttraumatic inflammation through actions on leuko-

TABLE 3. Postoperative Analgesic Consumption

	Fentanyl (μg)	Codeine (mg)		
Time	1 h	2–4 h	Day 1	Day 2
Morphine (G1)	130.0 ± 16.7	45.0 ± 14.3	50.0 ± 21.0 (95.0 ± 14.5)	33.3 ± 21.6 (128.3 ± 13.9)
Bupivacaine (G2)	21.4 ± 6.4	105.0 ± 22.2	120.0 ± 26.6 (225.0 ± 23.9)	84.5 ± 23.2 (309.5 ± 21.2)
Morphine + bupivacaine (G3)	31.8 ± 10.1	36.0 ± 5.7	66.0 ± 11.8 (72.0 ± 6.6)	33.0 ± 6.6 (105.0 ± 5.8)
Value	24.54	5.73	2.92	6.51
Value	<0.001	0.008	0.049	0.005
Post hoc	G1 > G2	G2 > G1	G2 > G1	G2 > G1
Comparison	G1 > G3	G2 > G3	G2 > G3	G2 > G3

The patients' total consumption during their stay in the recovery room (1 h), in the outpatient department (2–4 h), and at home (postoperative days 1 and 2) is given in means ± SEM. Data were analyzed by analysis of variance and Fisher's least significant difference procedure. Cumulative amounts of codeine are given in brackets.

cytes,[22,23] inhibition of bradykinin formation,[22] or inhibition of plasma extravasation.[24] On the other hand, opioid binding sites have been shown on primary afferent neurons.[25–27] We have demonstrated such receptors functionally[7] and immunohistochemically.[5] Conceivably, activation of these neuronal receptors can cause attenuation of the excitability or nociceptive input terminals[28–30] and/or inhibition of release of excitatory transmitters[31,32] and ultimately result in antinociception.

In summary, we have shown that in patients having undergone arthroscopic surgery, intraarticular bupivacaine yields postoperative analgesia of immediate onset but only of short duration (2–3 h), whereas intraarticular morphine produces an analgesic effect of delayed onset (about 2 h postinjection), but of remarkably long duration (as long as 2 days postoperatively). The combination of these two drugs results in satisfactory analgesia throughout the entire observation period.

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