Intraarticular morphine after arthroscopic ACL reconstruction

A double-blind placebo-controlled study of 40 patients

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ABSTRACT – We compared analgesic effects and pharmacokinetics of intraarticular versus intravenous administration of morphine after arthroscopic anterior cruciate ligament surgery. In a double-blind placebo-controlled study, 40 patients were randomly allocated to one of four treatment groups. Group I received 1 mg morphine intraarticularly and saline intravenously; group II received 5 mg morphine intraarticularly and saline intravenously; group III received 5 mg saline intraarticularly and morphine intravenously and group IV, the control group, received saline both intraarticularly and intravenously. The pain scores were significantly lower in groups I and II at 24 hours postoperatively than in group IV, and in group II during the rest of the postoperative period, as compared to groups III and IV. After intraarticular injection of 1 mg and 5 mg morphine, respectively, low concentrations of morphine-6-glucuronide (M6G) were found in the circulation, while morphine-3-glucuronide (M3G) appeared late after the injection in concentrations that considerably exceeded those of morphine in groups I and II.

The analgesic effect of intraarticular morphine together with the low levels of morphine and morphine-6-glucuronide in plasma further strengthens the view that opoids have a peripheral mechanism of action.

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Several studies have confirmed the effect of local morphine injections in animal experiments and clinical studies (Stein et al. 1991, 1993, Joshi et al. 1993, McSwiney et al. 1993, Haynes et al. 1994, Karlsson et al. 1995, Stein 1995, Brandsson et al. 1996). Intraarticular morphine has been used clinically to test the hypothesis that peripheral opioid receptors are upregulated by inflammation (Stein 1995). In such studies, intraarticular morphine doses of 1–5 mg have analgesic effects, which are superior to placebo (Kalso et al. 1997). The analgesic effect of morphine alone usually occurs late, but additive early effects can be obtained when an opioid is combined with a local anesthetic (Karlsson et al. 1995, Kalso et al. 1997).

Opioid receptors have been found on peripheral terminals of thinly myelinated and unmyelinated sensory nerves in animals (Hassan et al. 1993, Stein 1995) and humans (Stein et al. 1996). Opioid receptor messenger ribonucleic acid (mRNA) is located in the dorsal root ganglia (Schäfer et al. 1995). These findings support the theory that morphine not only is an analgesic but also has a putative anti-inflammatory action in peripheral tissues (Yaksh 1988, Barber and Gottschlich 1992, Stein 1995).

Thus, our principal aim in this study was to assess the analgesic effects of intraarticular versus systemic administration of morphine to patients undergoing arthroscopic ACL reconstruction surgery. To elucidate further whether a putative positive analgesic effect of intraarticularly administered morphine is central or possibly peripheral, we measured morphine and the M3G and M6G metabolites in plasma (Gong et al. 1991, 1992, Samuelsson et al. 1993, Wolff et al. 1995, 1996).

Patients and methods

40 consecutive patients (ASA status 1) with isolated chronic ACL insufficiency, who were undergoing arthroscopic reconstruction of the ligament, were included in the study. The Ethics Committee, Medical Faculty, University of Göteborg, approved the study procedure. Informed consent was obtained from all patients before surgery. The study was prospective, randomized and double-blind, controlled by an unbiased observer. At the end of the operation, the patients were randomized into one of four groups by sealed envelopes. The male:female ratio was 26:14 and the median age 24 (16–43) years.

Surgical procedure

The surgical procedure was standardized and similar in all patients. The ACL reconstruction was carried out using an arthroscopic one-incision technique. The central third of the patellar tendon (bone-tendon-bone) was used for ligament reconstruction, and the free graft was attached with interference screws at both ends. Only patients with isolated ACL insufficiency were included in the study. During surgery, a thigh tourniquet was inflated to 300 mm Hg and deflated at the end of the operation. The median duration of the surgical procedures was 81 (53–121) minutes. After the operation, the knee was rested in a knee brace, and motion between 10 and 90 degrees was allowed. No drainage was used. All patients were ambulated and discharged from the hospital as soon as possible. There were no intraoperative surgical complications.

Anesthetic regimen

Premedication with ketobemidon (Lundbeck) 5 mg was given intramuscularly approximately 30 minutes before starting surgery. Anesthesia was induced with intravenously administered thiopental (4–6 mg/kg body weight), after atropine 0.5 mg. The cuff of the tracheal tube was sprayed with lidocaine (Astra, 10 mg/dose), and tracheal intubation was facilitated by administering succinylcholine (1–1.5 mg/kg body weight). Anesthesia was maintained with spontaneous breathing of O_2/N_2O (1.5/3) and enflurane (1%–2%) supplemented by repeated small doses of meperidine (10 mg), the total amount not exceeding 75 mg. Blood pressure, electrocardiogram (ECG) and pulseoxymetry were continuously monitored peri-operatively and for approximately 3 hours postoperatively in the postanesthesia recovery unit. There were no complications from the anesthesia.

Study design

The patients were prospectively allocated into one of four groups. At the end of the operation, after all instruments had been removed from the knee and the wounds closed to minimize leakage, the patients received one of the following drugs or drug combinations intraarticularly and intravenously in a double-blind, randomized manner: a) 1 mg morphine sulfate in 20 mL saline intraarticularly and saline i.v. (n 10), b) 5 mg morphine sulfate in 20 mL saline intraarticularly and saline i.v. (n 10), c) 20 mL saline intraarticularly and 5 mg morphine sulfate i.v. (n 10). The fourth group (n 10) received 20 mL saline intraarticularly and 20 mL saline i.v. at the completion of the operation in the same manner. The doses of the drugs used had been chosen on the basis of previous clinical studies (Khoury 1990, Stein et al. 1991, Joshi et al. 1993, McSwiney et al. 1993, Haynes et al. 1994, Karlsson et al. 1995, Brandsson et al. 1996).

Pain assessment

The postoperative analgesia was assessed using a visual analogue scale (VAS), ranging from 0 (no pain at all) to 10 cm (worst possible pain) (Scott and Huskinsson, 1976). Pain scores were evaluated preoperatively (baseline) and at 2, 4, 6, 24, 48, 72, 96, 120, 144 and 168 hours after the operation. Supplementary analgesic medication was given on request and was noted during the 7 days after the operation. The total consumption of codeine and morphine for each group of patients during this period was calculated. Separate calculations were made for the 1st and 2nd postoperative days.

Pharmacokinetics

Blood was obtained from an antecubital vein before morphine injection and at 5, 10, 15, 30, 60, 120, 180 and 360 minutes after intraarticular or intravenous morphine administration (in the arm). Plasma was obtained after centrifugation and stored at minus 72 °C for subsequent analysis.

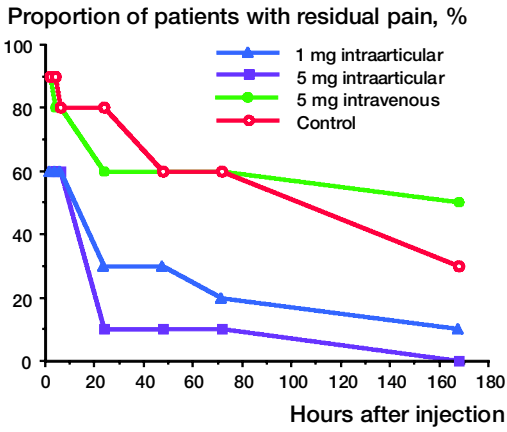

Figure 1. Effects of intraarticular (1 and 5 mg) or intravenous (5 mg) morphine and saline on postoperative pain in patients undergoing anterior cruciate ligament reconstruction. The proportions of patients with residual pain (i.e., VAS ≥ 2) are shown.

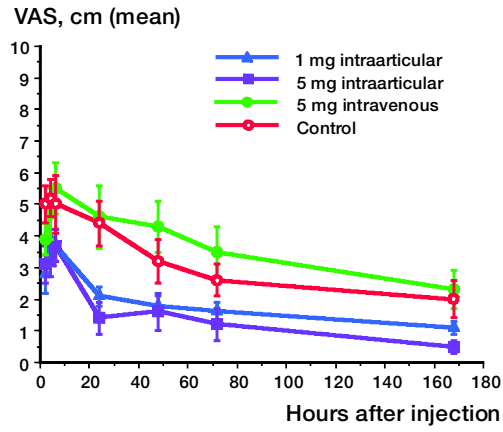

Figure 2. Effects of intraarticular (1 and 5 mg) or intravenous (5 mg) morphine and saline on postoperative pain in patients undergoing anterior cruciate ligament reconstruction. Mean values for the visual analogue score (VAS) are shown. The 5 mg intraarticular morphine group had significantly lower VAS ($p < 0.05$) than the 5 mg intravenous and control groups, after 24h (see text for more information).

Concentrations of morphine and its glucuronoide metabolites, M3G and M6G, were measured by reverse-phase high performance liquid chromatography (HPLC), as previously described (Svensson et al. 1982, 1986, Wolff et al. 1996). Tests of reproducibility showed that interassay coefficients of variance were 5% or less for the respective assays at concentrations which were twice those of the detection levels. The lowest measurable concentrations were 1 ng/mL, 3 ng/mL and 1 ng/mL for morphine, M3G and M6G, respectively. Pharmacokinetic parameters were calculated by standard methods (Gibaldi and Perrier 1982).

Statistics

Pain scores and supplementary analgesic requirements were compared using ANOVA, the Mann-Whitney U-test and Fisher's exact test. A p-value of less than 0.05 was considered significant. Median (range) was used when the VAS-score was analyzed and mean (SEM) when the morphine and the metabolite concentrations were analyzed.

Results

All randomized patients completed their participation in the study. The mean duration of the surgical procedure did not differ significantly between the groups.

Analgesic effects

Preoperatively there were no differences in pain scores between the groups. In group I, the median score was 0 (0–2.5), in group II 0 (0–0.5), in group III 0 (0–0.5) and in group IV 0 (0–4). After 24 hours, the pain scores were lower in the two intraarticular morphine treatment groups than in the control group (Figure 1). The pain score was significantly lower in the 5 mg intraarticular morphine group than in the intravenous and control groups during the whole postoperative period, i.e., from 24 hours to one week after surgery (Figures 1 and 2).

There were no significant differences in the need for of supplementary analgesics in the four groups either during the first 2 postoperative days (data not shown) or during the first postoperative week.

No complications or side effects occurred in any of the groups from intraarticular administration of the study drugs.

Pharmacokinetics

Intravenous administration of morphine resulted in peak plasma concentrations of 67 (14) ng/mL

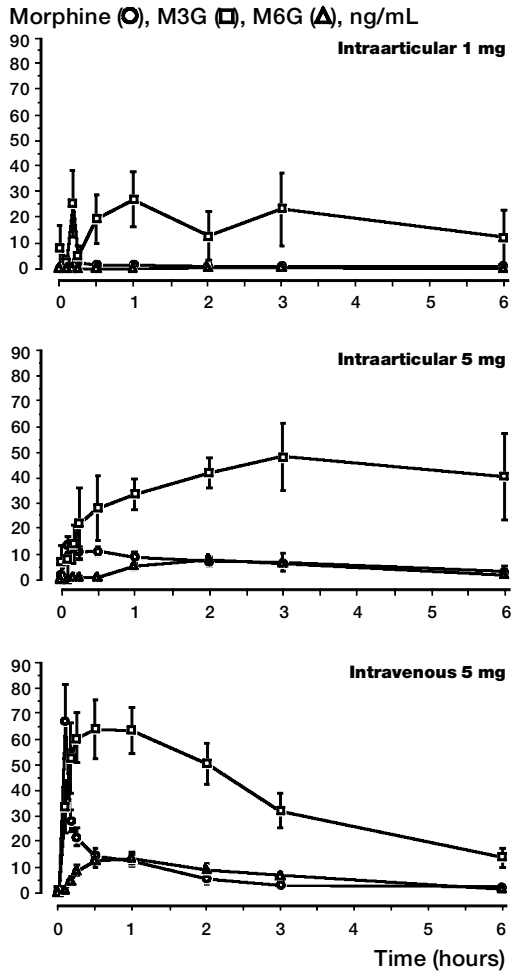

Figure 3. Plasma concentrations (mean ± SEM) of morphine and its major metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), in patients undergoing anterior cruciate ligament (ACL) surgery. Patients received either intraarticular (1 or 5 mg) or intravenous (5 mg) morphine postoperatively.

(mean (SEM)) immediately after the injection (Figure 3). The elimination half-life was 3.0 (0.9) hours. The M3G and M6G metabolites gradually increased in the systemic circulation after the intravenous morphine injection. Peak concentrations (Cmax 72 (10) and 14 (2) ng/mL, respectively) occurred within an hour after the injection (Tmax 0.6 (0.2) h and 0.8 (0.1) h, respectively).

Intraarticular administration of 1 or 5 mg of morphine resulted in almost immeasurable concentrations of morphine in plasma (Figure 3). Peak concentrations were 3.0 (0.6) ng/mL after 1 mg and 20 (3) ng/mL after 5 mg of morphine intraarticularly. Maximal concentrations (Cmax) of morphine in plasma after 5 mg and 1 mg intraarticularly were significantly (both $p < 0.05$) lower than Cmax after 5 mg of intravenous morphine. M6G was detected in low concentrations in the circulation up to 6 hours after intraarticular injection of the 5 mg and the 1 mg dose. Higher levels of the M3G metabolite were found in the circulation after intraarticular administration, although its concentrations were lower and it appeared more gradually in plasma than the M3G concentrations measured after intravenous administration of morphine (Table).

Discussion

The efficacy of intraarticular morphine has been documented in a number of studies and also been discussed in recent systematic reviews (Kalso et al. 1997, Stein and Yassouridis 1997). The data support the pain-relieving effect of intraarticular morphine after knee surgery. However, while convincing evidence for an early analgesic effect is lacking, there is more consistent evidence that intraarticular morphine provides a prolonged effect, with a reduction in pain intensity over 24 hours. We have recently shown (Karlsson et al. 1995, Brandsson et al. 1996) that the combination of intraarticular bupivacaine and morphine resulted in significant analgesia throughout the 48-hour period following ACL surgery.

As yet there is little evidence to support the hypothesis of peripheral opioid activation because hardly any randomized controlled trials have been done (Kalso et al. 1997). In our placebo-controlled study, we found a late and dose-related effect of intraarticular morphine alone, given as a single 1 mg or 5 mg intraarticular injection.

The concept of the presence of opioid receptors in peripheral tissues (Stein 1995) has resulted in a new rationale in the management of postoperative pain by giving opioids locally (Stein et al. 1991, Joshi et al. 1993, Stein et al. 1993, McSwiney et al. 1993, Haynes et al. 1994, Karlsson et al. 1995, Brandsson et al. 1996). In several controlled studies, low doses of peripherally-administered opioids reduce the activation of nociceptive afferents and local opioid administration has been shown to

Pharmacokinetics of morphine, mean (SEM) and range

	Morphine			M3G			M6G		
Morphine 1 mg i.a.									
AUC	5.5	(3)	0–31.3	99	(57)	7.9–583	1	(0.8)	0–8
C_{max}	3.0	(0.6)	0–6	40.1	(14)	9–129	0.6	(0.4)	0–4
T_{max}	0.7	(0.6)	0–6	1.15	(0.4)	0.2–3	0.5	(0.3)	0–3
Morphine 5 mg i.a.									
AUC	40	(13)	20–158	239	(66)	109–816	26	(2.6)	16–40
C_{max}	20	(3)	9–39	57	(16)	23–193	9	(0.8)	6–13
T_{max}	0.5	(0.3)	0.1–3	3.2	(0.5)	1.5–6	2	(0.2)	1–3
Morphine 5 mg i.v.									
AUC	41	(6)	1.5–70	203	(30)	47–345	37.7	(7)	0.0–88
t 1/2 λ_2	3	(0.9)	0.3–10.5						
C_{max}	67	(14)	6–173	72	(10)	16–136	14	(2)	0–30
T_{max}	0.1	(0)	0.1–0.1	0.6	(0.2)	0.1–2	0.8	(0.1)	0–1

AUC area under the plasma drug concentration-time curve (μg x h /L [0–6 h]),
t 1/2 λ_2 half-life (h) (elimination phase),
C_{max} highest drug concentration (ng/mL) observed in plasma,
T_{max} highest drug concentration-time (h) observed in plasma.

produce relatively long-lasting postoperative analgesia after knee arthroscopy and reconstructive ligament surgery (Joshi et al. 1993, McSwiney et al. 1993, Haynes et al. 1994, Karlsson et al. 1995, Brandsson et al. 1996, Kalso et al. 1997).

When assaying morphine and the active morphine metabolite M6G in plasma after intraarticular administration, only very low levels were found compared to those achieved after systemic administration. Attempts have been made to establish the levels of plasma morphine associated with analgesia after systemic administration. The minimum effective concentrations (MEC) of plasma morphine for relief of postoperative pain has been thought to be mean 16 (SD 9) ng/mL (Dahlström et al. 1982), but there is a wide variation (Glare et al. 1991). Thus in our study, the concentrations measured even after 5 mg of the intraarticular injection were too low to produce any significant systemic analgesic effect. These results support the view that the analgesic effect achieved by intraarticular morphine is due to a local effect in the peripheral tissue adjacent to the site of injection.

The exact mechanism by which local opioids reduce pain after peripheral administration is not yet fully known. However, an intriguing phenomenon is the enhanced efficacy of peripherally-applied opioids during conditions of inflammation. One possible explanation of this phenomenon is that opioid agonists have access to previously inactive neuronal opioid receptors, which become upregulated in the inflammatory milieu and thereby rendered active. In agreement with this, the peripherally-directed axonal transport of opioid receptors in nerve fibers is enhanced, which leads to an increase in their number (upregulation) on peripheral nerve terminals at later stages of the inflammatory process (Hassan et al. 1993, Schäfer et al. 1995).

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