Dose-dependency of intra-articular morphine analgesia

R. Likar1, S. Kapral3, H. Steinkellner2, C. Stein4 and M. Schäfer4*

1Abteilung für Anaesthesiologie und Intensivmedizin and 2Abteilung für Unfallchirurgie, Landeskrankenanstalten Klagenfurt, A-9026 Klagenfurt, Austria

Present addresses: 3Abteilung für Anaesthesiologie und Intensivmedizin, Allgemeines Krankenhaus Wien, Universität Wien, A-1090 Wien, Austria. 4Klinik für Anaesthesiologie und operative Intensivmedizin, Freie Universität Berlin, Universitätsklinikum Benjamin Franklin, Hindenburgdamm 30, D-12205 Berlin, Germany

*Corresponding author

We have examined if the analgesic effects of intra-articular morphine are dose-dependent in patients undergoing elective arthroscopic knee surgery. At the end of surgery, patients were allocated randomly to one of four groups to receive intra-articular saline (n=22), or morphine 1 mg (n=24), 2 mg (n=21) or 4 mg (n=19). After operation, patients remained in hospital overnight and pain intensity was assessed using a visual analogue scale at 1, 2, 3, 6, 9, 12, 18 and 24 h after intra-articular injection. Patients requesting additional analgesia received a loading dose of piritramide 0.1 mg kg–1 i.v. and were connected to a PCA device using the same drug. Increasing doses of intra-articular morphine were associated with greater analgesic effects and less supplementary analgesic requirements.

Br J Anaesth 1999; 83: 241–4

Keywords: analgesics opioid, morphine; analgesic techniques, regional, intra-articular; surgery, orthopaedic

Accepted for publication: January 7, 1999

Experimental studies have demonstrated the analgesic efficacy of peripherally applied opioid agonists in painful inflammatory conditions.1 Selective agonists for µ, δ and κ opioid receptors elicit such peripherally mediated analgesic effects.2 These effects are dose-dependent, stereospecific and antagonized by naloxone.2 Thus peripheral analgesic effects of opioids fulfill the criteria for opioid receptor specificity. Subsequently, opioid receptors were identified in subcutaneous tissue on peripheral nerve terminals of sensory neurones.3

The discovery that opioids can elicit analgesic effects by acting on peripheral opioid receptors has led to their examination in controlled clinical studies.4 5 The most consistent results have come from studies of intra-articular (i.a.) application of small, systemically inactive doses of morphine during arthroscopic knee surgery. The effects of this treatment on postoperative pain were evaluated by various direct (visual, numerical or verbal scales) and indirect (consumption of supplementary analgesics and time elapsed before the first request for supplementary analgesics) measures. Although in some studies postoperative pain relief after i.a. morphine was not superior to alternative treatments, other studies showed that i.a. morphine in doses of 0.5–5.0 mg resulted in significant reduction of pain.4 5 The analgesic effects could be antagonized by i.a. naloxone,6 but they were not greater in studies using higher doses of morphine. Three clinical studies assessed the analgesic effects of two different doses of morphine (without local anaesthetic) under similar conditions and did not show dose-dependency.6–8

In this study, we have examined, under standardized conditions, the analgesic effects of three different doses of morphine and saline administered into the knee joint after arthroscopic knee surgery.

Patients and methods

The study adhered to the ethical guidelines of the International Association for the Study of Pain9 and was approved by the Institutional Ethics Committee of the University Hospital in Graz, Austria. After having received detailed information about this study, patients gave written consent for participation.

We investigated 108 ASA I or II patients, aged 18–70 yr, weighing 50–90 kg, undergoing arthroscopic knee surgery (cruciate ligament injuries (28%), meniscal injuries (69%), instability of the knee joint (2%) and osteoarthritic changes of the knee joint (1%)). If patients were receiving analgesia, only those receiving non-steroidal anti-inflammatory drugs and those whose last intake was the night before surgery were recruited. Patients were excluded if arthroscopy was only diagnostic and no therapeutic interventions were made.
Patients were instructed on how to use the visual analogue scale (VAS) for pain rating, and the patient-controlled analgesia (PCA) device was demonstrated.

Patients were given oral midazolam 0.1 mg kg\(^{-1}\), 45 min before the start of anaesthesia. Anaesthesia was induced with propofol 2 mg kg\(^{-1}\), fentanyl 3 µg kg\(^{-1}\) and atracurium 0.5 mg kg\(^{-1}\) i.v., and maintained with 0.8–1.3% isoflurane and 65% nitrous oxide in oxygen. No other opioids were given during operation.

Test solutions of different concentrations of morphine (0.01, 0.02 and 0.04%) and isotonic saline were prepared and each bottle of test solution was coded either I, II, III or IV by the hospital pharmacy. When the surgical procedure was completed, 10 ml of the test solution were injected into the patient’s knee joint through the arthroscope. The tourniquet remained in place for another 10 min and was then released. If drains were placed into the knee joint, they were clamped for the first 60 min to prevent immediate loss of the injected test solution. Using a random number table, patients were assigned to one of four treatment groups in a double-blind manner: group I received saline 10 ml; group II received morphine 1 mg (0.01% solution); group III received morphine 2 mg (0.02% solution); and group IV received morphine 4 mg (0.04% solution). These doses were based on previous studies which have demonstrated an analgesic effect of i.a. morphine in patients undergoing similar arthroscopic knee surgery. The codes of the test solutions were broken at the end of the study.

Postoperative pain intensity was evaluated using a VAS extending from 0=no pain to 100=unbearable pain. VAS scales were always presented as unmarked lines that did not show previous notations of pain. VAS scores were recorded by a blinded observer at 1, 2, 3, 6, 9, 12, 18 and 24 h after the end of surgery. Patients were at rest when they were evaluated. If patients requested supplementary analgesics, piritramide was administered as an i.v. bolus dose of 0.1 mg kg\(^{-1}\).\(^{10}\) Patients were then connected to the PCA device (Graseby PC-3000) which was set to deliver an i.v. bolus dose of piritramide 2 mg. A lockout time of 8 min was used. The first time the patient required this ‘rescue’ medication and total analgesic consumption at the above intervals were documented.

The degree of sedation was assessed using a six-point scale (0=‘awake’ and 5=‘somnolent’). In addition, patients were asked if they experienced nausea, vomiting, pruritus or urinary retention. They were asked to grade symptoms from 0 to 3 (0=no symptoms, 1=mild, 2=moderate and 3=severe). Both sedation and adverse effects were assessed when the VAS was obtained at the stated intervals. The time of anaesthesia was determined as the time from induction of anaesthesia until the first verbal response to a command. Patients were given i.v. Ringer’s lactate solution, approximately 2 litre, over 24 h.

Statistical analysis
Patient data, sedation scores and the occurrence of adverse effects were analysed by analysis of variance (ANOVA) or chi-square test. To obtain the visual analogue score, we measured the distance in millimetres from 0 (no pain) to the mark provided by the patient. VAS scores are given as raw values (mean (SEM)). Supplementary analgesic consumption is shown as cumulative doses (mean (SEM)) of piritramide at each time. To test for dose-dependent effects of i.a. morphine on VAS scores, the area under the curve (AUC) for each dose of morphine was calculated using the trapezoid rule and a subsequent linear regression ANOVA was performed. \(P<0.05\) was considered significant.

Results
Of the 108 patients who entered the study, six were excluded because of open knee surgery and three because arthroscopy was only diagnostic. Six patients (two in each of groups I, II and III) refused further participation in the study because of severe opioid side effects (nausea and vomiting) which were clearly related to postoperative consumption of piritramide. Another seven patients were excluded (rejected further use of the PCA device (five patients) and infusion was paravascular and they refused another i.v. catheter (two patients)). Thus a total of 86 patients were included in the study (Table 1). There were no significant differences in age, weight, sex, duration of surgery or anaesthesia between groups (\(P>0.05\), ANOVA and chi-square test) (Table 1). The following surgical procedures were performed: meniscectomy (63%), shaving of damaged articular cartilage (30%), and repair and/or reconstruction of a cruciate ligament (7%). There were no differences between groups.

Maximum sedation scores during the study were never greater than 2, with the majority being 1 or less (Table 1). Differences between the four groups were not significant. Thirteen of 86 patients (one patient in group I; three in group II; five in group III; and four in group IV) reported minor side effects (primarily nausea) which were never rated higher than 1 (mild), and which occurred later than 6 h after the end of surgery.

VAS scores in all four groups were highest 1 h after operation and decreased continuously until 24 h (\(P<0.05\), ANOVA) (Fig. 1A). In addition, VAS scores in groups I, II and III were always higher than those in group IV (Fig. 1A). After calculating the area under each curve, there was a dose-dependent decrease in AUC from group I receiving saline to group IV receiving morphine 4 mg (\(P<0.05\), linear regression ANOVA) (Fig. 1B).

Cumulative piritramide consumption in all four groups was lowest 1 h after operation and increased continuously up to 24 h (\(P<0.05\), ANOVA) (Fig. 2). In addition, piritramide consumption was highest in group I and decreased with increasing dose of i.a. morphine (Fig. 2). Four patients in group I, three patients in group II and six patients each in groups III and IV did not request supplementary piritramide.

Time to first analgesic request of i.v. piritramide was
Table 1 Patient characteristics and maximum sedation scores in patients \( n=86 \) receiving different doses of intra-articular morphine at the end of arthroscopic knee surgery (mean (SEM) or range) or number). No significant differences

<table>
<thead>
<tr>
<th>Group I Morphine 0 mg</th>
<th>Group II Morphine 1 mg</th>
<th>Group III Morphine 2 mg</th>
<th>Group IV Morphine 4 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n )</td>
<td>22</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>39 (19–66)</td>
<td>39 (19–59)</td>
<td>40 (19–70)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81 (11)</td>
<td>73 (11)</td>
<td>78 (14)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>15/7</td>
<td>15/9</td>
<td>12/9</td>
</tr>
<tr>
<td>Time of surgery (min)</td>
<td>42 (21)</td>
<td>53 (30)</td>
<td>43 (17)</td>
</tr>
<tr>
<td>Time of anaesthesia (min)</td>
<td>72 (20)</td>
<td>87 (36)</td>
<td>71 (17)</td>
</tr>
<tr>
<td>Maximum sedation score (0–5)</td>
<td>0 (n=2)</td>
<td>0 (n=4)</td>
<td>0 (n=2)</td>
</tr>
<tr>
<td></td>
<td>1 (n=19)</td>
<td>1 (n=19)</td>
<td>1 (n=17)</td>
</tr>
<tr>
<td></td>
<td>2 (n=1)</td>
<td>2 (n=1)</td>
<td>2 (n=2)</td>
</tr>
</tbody>
</table>

Fig 1 Time course (A) and calculated area under the curve (AUC) (B) of VAS scores after intra-articular injection of saline and morphine 1 mg, 2 mg and 4 mg in patients undergoing arthroscopic knee surgery. Data are mean (SEM). VAS scores, as determined by AUC, decreased linearly with increasing dose of morphine \( (P<0.05, \text{ linear regression ANOVA}) \).

The lowest in group I and showed a tendency to increase with increasing doses of i.a. morphine (group I 79.4 (42.3) min; group II 122.1 (34.9) min; group III 99.3 (39.5) min; and group IV 188.5 (57.3) min). However, differences were not significant.

**Discussion**

Our results showed that patients who were allocated randomly to receive saline, or morphine 1, 2 or 4 mg i.a. at the end of arthroscopic knee surgery showed linearly decreasing VAS scores and self-administered less supplementary analgesics with increasing doses of i.a. morphine. Thus under standardized conditions, the analgesic effects of i.a. morphine increased with increasing dose.

This confirms results from controlled clinical studies showing the analgesic efficacy of i.a. morphine after arthroscopic knee surgery.\(^4\)\(^5\) Doses of 0.5–5.0 mg were used, a range in which systemic effects were excluded either by i.v. administration of the same dose of morphine in control groups\(^6\) or by measurement of plasma concentrations of morphine and its primary metabolites, morphine-3-glucuronide and morphine-6-glucuronide.\(^11\)\(^12\)

From animal work,\(^2\) one would predict that clinical studies using higher doses (e.g. 5 mg) of i.a. morphine would show greater pain relief than those using smaller doses (e.g. morphine 1 mg i.a.). However, this is not confirmed when comparing data from different studies.\(^6\)\(^13\)\(^14\)

The most likely explanation for this discrepancy is the great variability in study conditions, in particular differences in patient population, treatment regimen and intensity of surgical stimulation.

This provided the incentive for our study in which four different doses of i.a. morphine were compared under standardized conditions. Three previously published clinical studies compared different doses of i.a. morphine and did not demonstrate any dose-dependency of analgesic effects. In one, which was the first clinical study to successfully demonstrate the analgesic effects of i.a. morphine,\(^6\) the two doses chosen (0.5 and 1 mg) were probably too similar and group sizes too small to detect a statistically significant...
difference in analgesic effects. In another, morphine 2 and 4 mg i.a. were compared.\(^7\) Unfortunately, a control group receiving i.a. saline was not included and mean VAS scores for morphine 2 mg i.a. were already too low to detect further decreases with the higher dose of 4 mg.\(^7\) A third study showed paradoxically higher pain scores with morphine 2 mg compared with 1 mg i.a.,\(^6\) a result for which the authors did not give a plausible explanation. One difference from our study was that pain scores were obtained for 6 h and at 24 h after operation, while we recorded pain scores between 6 and 24 h (9, 12 and 18 h). Other studies which used different doses of morphine together with bupivacaine\(^{15} 16\) are not comparable because analgesic effects cannot be clearly attributed to morphine.

The enhanced efficacy of the analgesic effects of i.a. morphine in our study was further underscored by diminished supplementary analgesic consumption. The use of PCA allowed patients to individually self-administer supplementary piritramide to a pain level that was acceptable to them. This explains why VAS scores in the four groups converged at the end of the observation period.

The occurrence of opioid side effects (nausea, vomiting) causing six patients to drop out of the study was clearly related to self-administration of piritramide. This is in line with the majority of clinical studies describing no such side effects after i.a. administration of morphine,\(^5\) none of the other patients reported any serious side effects.

In summary, our results showed that, under standardized and controlled clinical conditions, increasing doses of i.a. morphine produced increasing analgesic effects after arthroscopic knee surgery. These findings are consistent with experimental studies in which peripheral opioid effects have been shown to be opioid receptor-specific.\(^2\) Furthermore, our results are in line with the recent identification of opioid receptors on peripheral sensory nerve terminals in human synovial tissue.\(^{18}\)

**Acknowledgement**

This study was supported in part by NIH/NINDS grant R01NS32466.

**References**