A Systematic Review of the Peripheral Analgesic Effects of Intraarticular Morphine

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The analgesic effects of intraarticular morphine are controversial. To systematically evaluate the effects, we performed a review of the literature and a meta-analysis of the peripheral effects of morphine injected intraarticularly. Research databases were searched to identify articles in which peripheral analgesic effects of morphine were studied in patients undergoing arthroscopic knee procedures under local, regional, or general anesthesia. The review was performed on three issues: does morphine injected intraarticularly produce analgesia, is it a dose-dependent effect, and, if so, is the effect systemic or mediated via peripheral opioid receptors? Visual analog score (VAS) and analgesic consumption were studied during the early phase (0–2 h), intermediate phase (2–6 h), and late phase (6–24 h) postoperatively after injection of morphine intraarticularly. Metaanalysis of these effect variables was performed by the weighted-analysis technique, and the essential homogeneity assumption was tested by the χ^2 test. Forty-five articles could be identified in which the effects of morphine were studied in a prospective, randomized manner, and 32 of these studies included a placebo control. Pooled analyses of data from 19 studies suitable for meta-analysis showed an improvement in analgesia after morphine compared with placebo in the order of 12–17 mm on the VAS during all three phases of treatment. Studies with high quality scores showed somewhat smaller improvements. Total analgesic consumption could not be analyzed statistically, but the number of studies showing decreased analgesic consumption or no differences between groups was identical (six and six). No clear dose-response effect was seen when VAS was used as a measure of pain, but it was seen when area under the curve was used as a measure of pain. A systemic effect of peripherally-injected morphine was not possible to exclude because of the very limited data available. We conclude from this metaanalysis that intraarticularly administered morphine has a definite but mild analgesic effect. It may be dose dependent, and a systemic effect cannot be completely excluded.

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The effects of morphine on peripheral receptors were first studied in animals, and it was found to have analgesic effects in a rat model of acute inflammation (1). Stein et al. (2) showed that the effects of morphine injected peripherally intraarticularly were mediated by peripheral opioid receptors, because the analgesic effect could be reversed by the intraarticular injection of naloxone. These studies were first published in the early 1990s, and since then a large number of articles have been published on the peripheral effects of morphine. Morphine and other opioids have been injected in the vicinity of practically every peripheral nerve and many joints to assess its analgesic efficacy.

Kalso et al. (3) published a qualitative systematic review of the literature on the intraarticular effects of morphine in 1997. It is surprising that they found only four studies that scored more than four points on a five-point qualitative scale described by McQuay and Moore (4). Accordingly, no metaanalysis was performed because of a lack of an adequate number of high-quality studies. They concluded that morphine probably has mild analgesic effects when injected intraarticularly in humans but also recommended further randomized controlled trials (RCTs) to clarify the issue. The primary aim of this systematic review was to establish whether morphine injected intraarticularly has an analgesic effect when compared with placebo. The secondary aims were to assess whether this is a dose-dependent effect, and if so, whether it is a systemic effect or occurs via peripheral receptors.

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This systematic review was consequently performed in four steps: 1) We reviewed all studies published in the literature in which a direct comparison was made between morphine and placebo injected intraarticularly in humans; 2) we performed a qualitative analysis of these studies on the basis of the criteria recommended by McQuay and Moore (4); 3) we then performed a quantitative analysis of the data from all randomized, placebo-controlled trials and also a quantitative analysis of studies with a high quality; and 4) as a last step in the analysis, those studies in which different doses of morphine were given were also analyzed to see whether there was a dose-dependent effect of morphine. If a dose-dependent effect was seen, we were interested in determining whether this was a systemic effect or an effect via peripheral morphine receptors.

Methods

A systematic search of the literature was performed by first identifying key words related to the subject (opiate/opioids, morphine, articular, arthroscopy, analgesia, pain, postoperative) and then searching the MEDLINE database between the years 1986 and 2000 for original publications, review articles, abstracts, case reports, and letters to the editor. The reference list in every article published on this subject was screened for references that may have been missed in the MEDLINE database. The reference list of review articles, including a previously published systematic review (3), was also searched. Finally, the Cochrane Foundation database and EMBASE were also searched. No attempt was made to obtain access to unpublished studies from authors who have previously published on this subject. Three of the authors reviewed the results in detail. One of us had previously published articles on this subject, one had a special interest in the area but had not published on this subject, and the third was an independent reviewer with no special interest in this field. We agreed on the following inclusion/exclusion criteria when considering each study.

1. Only studies of humans (volunteers and patients) were included.
2. Only randomized and prospective studies were considered (Level 1 evidence).
3. Studies in which the primary aim was to assess the effect of tourniquet time on postoperative analgesia were excluded (5,6).
4. Those studies in which the primary aim was to assess the effects of intraarticular morphine on chronic pain were also excluded (7,8).
5. Two studies in which the authors compared regional nerve blocks with intraarticular analgesics for postoperative pain relief after arthroscopy were also excluded (9,10).
6. Only those studies in which morphine was injected into the knee joint were included.

In the assessment of postoperative pain, three phases were identified.

1. The early phase, 0–2 h: during this phase, the residual effects of intraoperative analgesics could result in study bias (regional or local anesthesia) (11–14). Thus, studies in which intraoperative narcotics were used could result in study bias when compared with narcotic-free anesthesia during this early phase.
2. The intermediate phase, 2–6 h: during this phase, the effects of local anesthetics and perioperative opioids and the residual effects of premedicants usually diminish.
3. The late phase, 6–24 h: the analgesic effects seen during this phase are most likely to be the effects of intraarticular morphine alone.

Two measures of pain relief were analyzed:

1. Direct measure: the visual analog score (VAS) at rest, with no pain = 0 and worst imaginable pain = 10, was recorded in each study. The exact pain score was somewhat difficult to decipher in some studies in which results were presented in figures (versus tables). Thus, two of the authors independently estimated the VAS presented in the figures in each article and came to an agreement on the mean ± SEM or SD VAS. When multiple measures of VAS were presented in each phase, the median VAS pain score was used in the final metaanalysis.
2. Indirect measure: the total consumption of analgesics after surgery was recorded in each study. However, many studies did not present the exact doses consumed. The number of different postoperative analgesic regimens was large and could not be subjected to any statistical analysis. Consequently, we have summarized our findings only if they were significantly different in each study. No further statistical tests were used.

In view of the large number of studies published and the uncertainty of the conclusions drawn, our review was limited to answering three main questions: 1) Does morphine have any analgesic effect when injected intraarticularly compared with a control group receiving only placebo? 2) If there is an analgesic effect, is it dose dependent? 3) Is the possible analgesic effect systemic or local (peripheral)? Thus, studies in which morphine was not compared directly with placebo were excluded from the review.

Means and 95% confidence intervals (CI) for the difference (treatment − control) in pain score on the VAS were calculated from the studies identified.

The formulas for two independent samples with unequal variances were used according to Welch (15). The CIs were plotted with VAS in millimeters on the horizontal axis, and different individual studies were plotted on the vertical axis. Means located to the left of the reference line 0 indicate that treatment is superior to placebo, whereas mean values to the right indicate the opposite.

Metaanalysis was performed with the weighted-analysis technique based on that of Grizzle et al. (16) and as described by Greenland (17). The study weights used in combining the results from the different studies were the inverse variance computed from the estimated standard error, 1/SE (2), where the formula for SE was given by Welch (15). We tested the essential homogeneity assumption by the χ^2 test described by Greenland (17), and when homogeneity was rejected, we calculated the final CI for the summary effect with a correction based on random effect modification, also described by Greenland (17). All computations could be implemented by standard statistical software, SPSS (18), with additional commands using the internal syntax of the package. The final 95% CIs were visualized graphically in the same way as the CIs of the basic studies. The analysis was performed for all 19 studies suitable for metaanalysis as well as for those studies that had a higher quality score.

Results

Forty-five articles could be identified in which the authors had specifically studied the effects of morphine injected intraarticularly into the knee joint in humans in a prospective, randomized way. Of these, 32 studies had included a placebo control, whereas 13 used an active drug in the control group. The active control group could be either a local anesthetic or morphine injected IV or IM. Where an active drug was injected IV or IM, we included only those studies in which this was double-blinded.

Twenty-seven studies could be identified in which morphine was compared directly with placebo (normal saline) in patients undergoing arthroscopic knee surgery (Table 1). A total of 1748 patients were studied. Thirteen of these studies found a beneficial effect of morphine (19–31), whereas 14 others did not find any beneficial effect (11–13,32–42). In one study (42), no beneficial effect of morphine was found when all patients were included, but significantly better analgesia was provided when a subgroup of patients with VAS pain intensity >10 mm was analyzed. General anesthesia was used in 12 of the 13 studies that showed a beneficial effect of morphine, and in one study, local anesthesia was used for the operative procedure. Ten of the 13 studies used intraoperative tourniquet, and in 8 studies, intraoperative narcotics were given as a part of the anesthetic technique. In nine studies in which 4–10 mg morphine was injected intraarticularly, better analgesia was reported in the morphine groups compared with the placebo group. In six studies, a dose of 1 mg morphine was injected intraarticularly (in two studies, two different doses of morphine were given). Of these, two studies found no benefit of 1 mg morphine compared with placebo (34,38), and of the four studies in which VAS was less in the morphine group, one study found this to be less only between 0 and 2 h (Phase I) (20), whereas the other three found it to be less between 6 and 24 h (Phase III) (24,28,31).

Nineteen studies could be identified in which the data were presented in a way that could be used in a metaanalysis. In the other studies, no SD or SEM was given (22,26,35–38), median and range were presented (39) instead of mean and SD, or results were presented as change from baseline values (13). These studies could not be included in the metaanalysis. The results of the 19 studies are shown in Figures 1–3 for the early, intermediate, and late phases. There was a mean reduction in pain intensity in the morphine group compared with placebo during each of the three phases. The mean (95% CI) of this reduction was 11.6 (6.6–16.6) mm, 17.0 (11.7–22.3) mm, and 14.7 (9.2–20.2) mm during Phases I, II, and III, respectively, when all 19 studies were included in the analysis (Table 2). Of the 13 studies in which beneficial effects of morphine were found, 6 found significantly less analgesic consumption in the morphine group, whereas 6 found no significant difference between the groups. One study stated differences in analgesic consumption but did not state whether these reached statistical significance.

Metaanalysis of high-quality studies was performed (score ≥3 and ≥4) to see whether the quality had an effect on the heterogeneity and on the difference between placebo and treatment groups. Homogeneity was present only when quality scores ≥4 were analyzed and only during the early (0–2 h) and intermediate (2–6 h) phase (Table 2). In this latter group with a high quality score, the treatment group continued to show better analgesia than the placebo group. However, the differences between the treatment and placebo groups were less than when all studies were included.

Seven studies could be identified in which the authors studied a dose-response relationship for the effects of morphine injected intraarticularly (Table 3). A total of 613 patients were studied in these seven studies. In two studies, 5 mg morphine was found to be better than 1 mg during the first 24 h after surgery (24,29). In the other four studies, there were no advantages in giving 1 mg compared with 0.5 mg of morphine (2), 1 mg compared with 2 mg of morphine (37,42), 2 mg morphine compared with 5 mg (39), or

Table 1. Randomized, Double-Blinded Placebo-Controlled Studies

Reference No.	Author	No. Patients (groups)	Type of operation	Type of anesthesia	Tourniquet	Morphine dose (mg)	Duration of observation	Conclusion	Quality (Ref. 4)
11	Heard et al. (1992)	139 (3)	Arthroscopy	112 GA 27 RA	No	3	24 h	Morphine = placebo	3
12	Raja et al. (1992)	47 (3)	Arthroscopy	Epidural	Yes	3	6 h	Morphine = placebo	4
13	Gupta et al. (1999)	100 (5)	Arthroscopy	LA	No	3	48 h	Morphine = placebo	2
19	Joshi et al. (1993)	20 (2)	ACL repair	GA	Yes	5	24 h	Morphine better	2
20	Joshi et al. (1993)	40 (4)	Arthroscopy	GA	Yes	5	24 h	Morphine better	2
21	Lyons et al. (1995)	66 (3)	Arthroscopy	GA	Yes	5	24 h	Morphine better	3
22	Haynes et al. (1994)	40 (4)	Arthroscopy	GA	Yes	1	24 h	Morphine better	3
23	Cepeda et al. (1997)	112 (4)	Arthroscopy	GA	Yes	10	72 h	Morphine better	5
24	Kanbak et al. (1997)	35 (3)	Arthroscopy	GA	Yes	1 and 5	24 h	Morphine better	2
25	Joshi et al. (1993)	20 (2)	ACL repair	GA	Yes	5	24 h	Morphine better	2
26	Dalsgaard et al. (1994)	52 (2)	Arthroscopy	LA	?	1	24 h	Morphine better	3
27	Jaureguito et al. (1995)	40 (3)	Arthroscopy	LA	No	4	24 h	Morphine better	3
28	Joshi et al. (1992)	20 (2)	Arthroscopy	GA	Yes	5	24 h	Morphine better	2
29	Richardson et al. (1997)	106 (3) 48 (3)	Arthroscopy	GA	?	1 and 5	24 h	Morphine better	3
30	Chan (1995)	40 (4)	Arthroscopy	GA	Yes	1	24 h	Morphine better	3
31	Karlsson et al. (1995)	40 (4)	ACL repair	GA	Yes	1	48 h	Morphine better	4
32	Dierking et al. (1994)	33 (2)	Arthroscopy	GA	No	2	6 h	Morphine IA = IM	4
33	De Andres et al. (1998)	103 (4)	Arthroscopy	GA	Yes	1	24 h	Morphine better	4
34	Wrench et al. (1996)	60 (3)	Arthroscopy	GA	Yes	1	2 h	Morphine = placebo	4
35	Söderlund et al. (1997)	70 (7)	Arthroscopy	GA	Yes/No	1	24 h	Morphine = placebo	3
36	Aasbo et al. (1996)	107 (4)	Arthroscopy	GA	Yes	3	7	Morphine = placebo	3
37	Ruwe et al. (1995)	124 (5)	Arthroscopy	GA	Yes	1 and 2	48 h	Morphine = placebo	5
38	Gatt et al. (1998)	30 (3)	ACL repair	GA	?	1	2 h	Morphine better	4
39	Hege-Scheuing et al. (1995)	59 (2)	Arthroscopy	GA	?	1	24 h	Morphine IA = IV	3
40	Laurent et al. (1994)	58 (3)	Arthroscopy	GA	?	2 and 5	36 h	Morphine = placebo	4
41	Björnsson et al. (1994)	78 (4) 71 (3)	Arthroscopy	GA	No	1 and 5	24 h	Morphine = placebo	2
42	Rosseland et al. (1999)	90 (3)	Arthroscopy	LA	?	1 and 2	48 h	Morphine = placebo	5

Studies in which morphine injected intraarticularly was compared with placebo (normal saline) in a randomized, double-blinded design.
GA = general anesthesia; RA = regional anesthesia; LA = local anesthesia; IA = intraarticular; ACL = anterior cruciate ligament.

1 mg versus 3 mg of morphine (43). In one study, varying doses of morphine (1, 2, and 4 mg) were compared with placebo (44). The authors found a dose-response reduction in pain intensity as measured by the area under the curve, but not as measured by the VAS.

Six studies compared intraarticular versus IV or IM morphine to exclude systemic effects of morphine given intraarticularly (Table 4). In all, 467 patients were studied. Three studies found no differences in VAS scores after surgery between the intraarticularly and systemically-administered morphine (29,32,39), whereas two studies found lower pain scores in patients receiving a similar dose of morphine IV (2,28). In one of these two studies, a lower pain score was seen during Phase III and not Phase I or II after surgery (28). In the sixth study, the authors found no significant differences between intraarticular and IM morphine in a dose of 5 mg, but this study was not blinded (41). Plasma concentrations of morphine were measured after intraarticular injections of 1 and 5 mg morphine in one study (28) and after IV and intraarticular injection (5 mg) in another study (29). The plasma concentration of morphine 2 h after 5 mg morphine intraarticularly was approximately 50% of the concentration achieved after IV injection (29). In the other study (28), of the 10 patients studied, 2 had spuriously large concentrations and 2 others had undetectable levels (<1 ng/mL). In the remaining six patients, the authors found smaller concentrations of morphine than are usually described after systemic morphine. Plasma concentrations of morphine-3-glucoronide, however, were approximately 13 ng/mL 90–120 min after intraarticular administration of morphine (29).

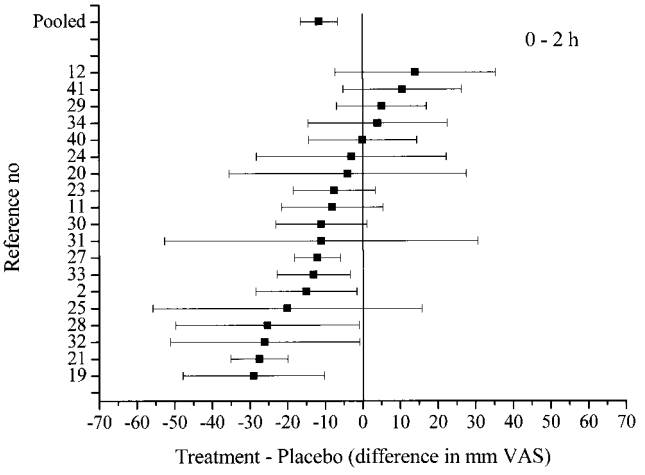

Figure 1. Early phase; x axis = mean and confidence interval (CI) of the visual analog scores (VAS) at 0–2 h in the different studies; y axis = reference number for the study. Pooled data from all studies are depicted at the top.

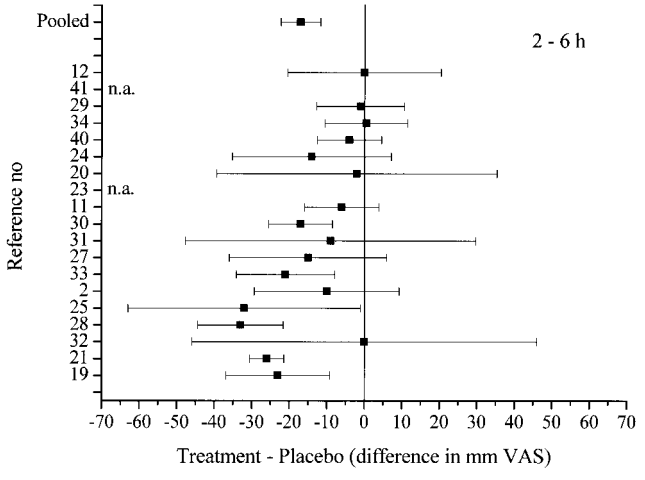

Figure 2. Intermediate phase; x axis = mean and confidence interval (CI) of the visual analog scores (VAS) at 2–6 h in the different studies; y axis = reference number for the study; n.a. = not available. Pooled data from all studies are depicted at the top.

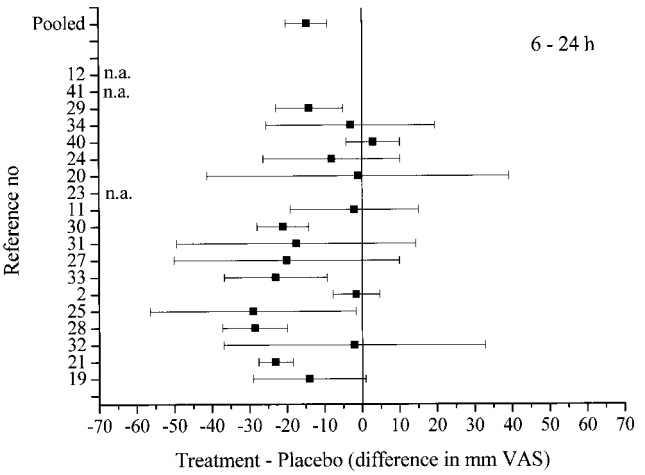

Figure 3. Late phase; x axis = mean and confidence interval (CI) of the visual analog scores (VAS) at 6–24 h in the different studies; y axis = reference number for the study; n.a. = not available. Pooled data from all studies are depicted at the top.

Discussion

In this systematic review of the intraarticular effects of morphine, we found that morphine produced a definite reduction in postoperative pain intensity compared with placebo, and this was seen during all postoperative phases. The effect was mild (mean reduction in pain intensity, 12–17 mm on the VAS scale). This effect could be dose dependent, but a systemic effect of the intraarticularly administered morphine cannot be completely eliminated.

We used more liberal inclusion criteria in our meta-analysis; i.e., all RCTs in which the results could be statistically analyzed were included and not just those with high quality scores. To ensure that an RCT is of high quality, McQuay and Moore (4) suggest that the study should be 1) randomized, and that the method of randomization should be described and appropriate; 2) double-blinded, and the method of blinding should be described and appropriate; and 3) any withdrawals from the trials should be described. Many of the studies described in the literature may have followed these criteria but may not have stated it in the study report. Should these studies then be excluded from a metaanalysis? A similar argument was put forward by Fisher (45), who stated that well designed studies might be rejected simply because the authors failed to specify certain criteria demanded by the metaanalyst (and such criteria might have been standard practice at the time the study was conducted but were not routinely reported). By using more liberal inclusion criteria, we were able to draw conclusions from a larger number of studies (and patients). The conclusions should, however, carry a warning that we do not know whether the authors have strictly followed the methodology of high-quality trials, but we have no reason to believe otherwise.

Studies in which morphine was compared with a local anesthetic, a nonsteroidal antiinflammatory drug, clonidine, or another narcotic analgesic, but not a placebo group, were excluded. Although Kalso et al. (3) argue that the highest hierarchy of evidence is when local anesthetic is used intraarticularly because local anesthetics are known to provide reliable analgesia of predictable duration, a systematic review of intraarticular local anesthetics found only weak evidence for reduction of postoperative pain after arthroscopic knee surgery (46). Also, combining local anesthetics with morphine or a nonsteroidal antiinflammatory drug may result in interactions and

Table 2. Results of Metaanalysis with Stratification for Quality Score

Quality scoring	*n*	0–2 h	2–6 h	6–24 h	Heterogeneity among studies[a]
All studies	19	−11.6 ± 5.0	−17.0 ± 5.3	−14.7 ± 5.5	Yes
Quality score ≥3	13	−11.8 ± 5.6	−15.5 ± 6.2	−13.4 ± 6.6	Yes
Quality score ≥4	7	−6.7 ± 5.5	−5.7 ± 5.4	−3.0 ± 10.0	No/yes[b]

VAS = visual analog score; Difference between treatment and placebo in mm VAS, supplemented with 95% confidence interval.
[a] For discussion of heterogeneity, see text.
[b] Homogeneity for 0–2 h and 2–6 h, heterogeneity for 6–24 h.

possible synergistic effects, thus confounding the conclusions drawn. Thus, the primary aim of this systematic review was to quantify the effect of morphine versus placebo and not versus an active drug.

Results from many studies are presented only as graphs or diagrams, and sometimes it is difficult to identify the exact value of the studied variable. For instance, VAS was often presented as a diagram, with time on the *x* axis and pain intensity (cm) on the *y* axis. Because resolution of the *y* axis was sometimes poor (e.g., intervals of 2 cm on the scale, absence of marks representing digits, or three-dimensional figures) (38,24), it was sometimes impossible to identify the correct pain intensity score at a given time point. All studies in which two independent authors were in agreement on the possibility of extraction of data from figures are included in the metaanalysis.

Although McQuay and Moore (4) do not discuss statistical problems when evaluating high-quality articles, this is one of the most common problems in RCTs. One of the problems encountered was that one of the authors used two different statistical methods for the same data and showed that, depending on the statistical method used, the result could be significant ($P < 0.05$) or not significant ($P > 0.05$) (22). Some authors have presented CIs without mean values (23), others have presented mean values without SD, SEM, or CI (26,38), and still others have presented only changes from baseline values rather than actual values (13). Most of these studies could not, unfortunately, be used in any constructive metaanalysis, thus limiting the number of studies suitable for analysis.

The above-mentioned problems deal with the selection of studies suitable for the metaanalysis. As for the analysis itself, we found a significant heterogeneity between the studies when all studies were included in the analysis. This means that the studies do not estimate a common, constant difference between placebo and treatment. Instead, there seems to be a variation in the difference that is more than that of simple random variation. The variation can be caused by characteristics that differ between the studies and at the same time affect the treatment. The interpretation of the summarized mean values is in this case a bit more complex. They now represent means in the distribution of the differences rather than a simple variable. By excluding some of the studies from the metaanalysis, in particular those with effect-related study characteristics, homogeneity could possibly have been achieved. This was found to be true when only high-quality studies were included in the metaanalysis (score ≥4). The relatively small number of available studies speaks against this approach, and because in our case the calculated mean values were found in the region in which treatment was superior to placebo and the CIs were narrow, we believe that the heterogeneity does not in any essential way contradict the main conclusions of the metaanalysis. In addition, as stated by Greenland (17), the analysis of heterogeneity can be the most important result of a metaanalysis.

The major issue in this systematic review was to establish whether morphine injected intraarticularly has an analgesic effect when compared with placebo. Thus, we included only studies that were prospective, randomized, and double-blinded. The subsequent metaanalysis showed a reduction in pain intensity by a mean value of 12–17 mm on VAS during the three postoperative phases. This confirms the early findings of Khoury et al. (7) that morphine injected intraarticularly produces analgesia. Taking into account that morphine receptors have been described on peripheral nerves in animals (47) and humans (48), one may conclude that morphine also acts via peripheral receptors to induce analgesia in humans. However, these results lead to further questions that must be answered. Why do some studies show a good effect of morphine injected intraarticularly and others do not? Is the effect dose dependent? Is this a systemic effect or an effect on peripheral receptors?

According to our systematic review, there seems to be wide variability in the analgesic effects when morphine is injected intraarticularly. This variability is seen not only between studies (population variability), but also within studies (patient variability). In addition, lack of consistency is seen between studies, i.e., some studies report early beneficial effects of morphine, whereas others show only late effects. Factors that might affect the results could include the type of surgery and pain intensity, preexisting inflammatory reaction, and when the tourniquet was released, as well as study design (underpowered studies may result in negative results). There is little doubt that the

Table 3. Dose-Effect Relationship

Reference No.	Author	No. Patients (groups)	Type of operation	Type of anesthesia	Tourniquet	Morphine dose (mg)	Duration of observation (h)	Conclusion	Quality (Ref. 4)
2	Stein et al. (1991)	52 (4)	Arthroscopy	GA	—	0.5 and 1	24	Morphine 1 mg better	3
24	Kanbak et al. (1997)	35 (3)	Arthroscopy	GA	Yes	1 and 5	24	Morphine 5 mg better	2
29	Richardson et al. (1997)	106 (3) 48 (3)	Arthroscopy	GA	—	1 and 5	24	Morphine 5 mg better	3
37	Ruwe et al. (1995)	124 (5)	Arthroscopy	GA	Yes	1 and 2	48	Morphine 1 mg = 2 mg	5
42	Rosseland et al. (1999)	90 (3)	Arthroscopy	LA	—	1 and 2	48	Morphine 1 mg = 2 mg	5
43	Tetzlaff et al. (1999)	30 (3) 49 (4)	ACL repair	GA	—	1 and 3	4	Morphine 1 mg = 3 mg	4
44	Likar et al. (1999)	102 (4)	Arthroscopy	GA	Yes	1, 2, and 4	24	Morphine 4 mg >2 mg >1 mg	5

Studies in which the effect of varying doses of morphine injected intraarticularly were compared in a dose-response design.
GA = general anesthesia; LA = local anesthesia; ACL = anterior cruciate ligament.

Table 4. Intraarticular Versus Systemically-Administered Morphine

Reference No.	Author	No. Patients (groups)	Type of operation	Type of anesthesia	Tourniquet	Morphine dose (mg)	Duration of observation (h)	Conclusion	Quality (Ref. 4)
2	Stein et al. (1991)	52 (4)	Arthroscopy	GA	—	0.5 and 1	24	Intraarticular better	3
28	Joshi et al. (1992)	20 (2)	Arthroscopy	GA	Yes	5	24	Intraarticular better	2
29	Richardson et al. (1997)	106 (3) 48 (3)	Arthroscopy	GA	—	1 and 5	24	Intraarticular better	3
32	Dierking et al. (1994)	33 (2)	Arthroscopy	GA	No	2	6	Morphine IA = IM	4
39	Hege-Scheuing et al. (1995)	59 (2)	Arthroscopy	GA	—	1	24	Morphine IA = IV	3
41	Björnsson et al. (1994)	78 (4) 71 (3)	Arthroscopy	GA	No	1 and 5	24	Morphine IA = IM	2

Studies in which the effects of intraarticular morphine were compared with systemically administered morphine.
GA = general anesthesia; IA = intraarticular.

presence of preexisting inflammatory reaction increases the efficacy of intraarticular morphine (48). The role of the tourniquet is more controversial. Two studies that specifically addressed this issue reported contradictory results (5,6), and the mechanism for the potential positive effect of tourniquet remains unclear. The hypothesis that the presence of tourniquet would improve the binding of morphine to the intraarticular receptors is not proven (5).

Many studies with negative results seem to be too small (underpowered) to detect significant differences. Because pain intensity in many studies is modest, large sample sizes are required to reliably detect significant differences. Thus, studies in which pain intensity is more pronounced (anterior cruciate ligament repair) and in which there is preexisting inflammation (e.g., chronic arthritis) may more likely detect significant effects with smaller sample sizes. This was, in fact, the observation made by Rosseland et al. (42) when they excluded patients with minimal pain. They found that there was a significantly better effect of morphine compared with placebo.

Another issue to be addressed is whether the potential effect of intraarticular morphine is dose dependent or not. Once again, the results are equivocal, with some studies suggesting a dose-dependent effect while others do not. A well-designed study of high quality showed a dose-dependent analgesic effect after intraarticular morphine (44). Three doses of morphine (1, 2, and 4 mg) injected intraarticularly after arthroscopy performed under general anesthesia were compared with placebo. Although no statistical differences were shown between the groups in the VAS pain scores, the area under the VAS pain curve decreased with increasing doses of morphine. Similarly, although no differences were seen in analgesic consumption at specific time points, the overall cumulative analgesic consumption decreased with increasing doses of morphine. Thus, this study showed that the analgesic effect of morphine is dose dependent. It is, however, possible that the peak effect of morphine was not seen after 4 mg and that a further increase in the dose would provide better analgesia. Kalso et al. (3) argued that doses of 1 mg morphine, when diluted to 20 mL and injected into the knee joint, would produce concentrations (in the knee) of more than 1000 times that seen after the systemic injection of morphine. This suggests that the peripheral opioid receptors should be fully saturated with 1 mg morphine in 20 mL saline. Yet Likar et al. (44) found a dose-dependent analgesic effect of morphine injected intraarticularly. One explanation for these contradictory findings might be that the analgesic effect of morphine is due to its systemic absorption after intraarticular injection. In contrast to the findings of Likar et al. (44), a study compared the effects of 1 vs 2 mg morphine and found that patients receiving morphine 2 mg had more pain than those receiving 1 mg (43). Two other studies had similar results. Björnsson et al. (41) found higher pain scores than placebo during the first 2 h after the injection, although the difference did not reach statistical significance. Similarly, Gupta et al. (13) also found higher pain scores during the first 2 h in the morphine group after 3 mg morphine. Morphine causes histamine release, and this may be the mechanism for the short-lasting local hyperalgesia seen in some studies. In another study, Rosseland et al. (42) found no improved analgesia when comparing 1 vs 2 mg of morphine intraarticularly. The reasons for these conflicting results are unknown.

In three studies, no differences were found in VAS scores between the systemic and intraarticular groups, whereas in two studies intraarticular morphine was found to be better than IV. In the latter two, no differences in VAS scores were seen during the first two to four hours after the injection. However, better analgesia was reported during the next 24 hours in the group receiving intraarticular morphine. Thus, it seems that the analgesia is prolonged when morphine is injected intraarticularly, whereas systemic morphine has a short duration of effect. It has been proposed that glucoronidation of morphine intraarticularly may produce morphine-6-glucoronide, which has a longer half-life that may account for the more prolonged effect (28). In the same study, plasma morphine-6-glucoronide and morphine-3-glucoride concentrations were measured after the injection of 5 mg of intraarticular morphine, and it was found that the latter was quite large. The plasma concentration of morphine was measured after systemic and intraarticular administration in two studies (28,29). Whereas Joshi et al. (28) found that the plasma concentrations were small during the sampling period (up to four hours), Richardson et al. (29) found a mean plasma concentration of 3.5 ng/mL two hours after intraarticular administration of 5 mg morphine, and a systemic dose of 5 mg morphine produced a concentration of 6.3 ng/mL—approximately twice as much after IV compared with intraarticular morphine. This is somewhat surprising because one would not have expected such large plasma concentrations after the intraarticular injection of morphine; it makes one wonder whether this effect is, after all, a systemic effect. No studies have measured plasma concentrations after 6–24 hours of intraarticular administration of morphine when the analgesic effect of morphine (intraarticular) appears to be maximal. Could there be an axonal flow of morphine via peripheral nerves into the spinal fluid and the analgesic effects of morphine seen are via spinal receptors (and not peripheral morphine receptors), causing the delayed effect? Future studies should focus on the role of inflammation in producing peripheral analgesia

and also on whether the analgesic effect of morphine is via opioid receptors or via inhibition of prostaglandin mechanisms in inflamed tissues.

Metaanalysis of the studies available in the literature has shown that morphine injected into the intraarticular space produces analgesia up to 24 hours after the injection, and this could be a dose-dependent effect. Whether the effect is via peripheral opioid receptors or a systemic effect remains to be shown conclusively.

References

1. Joris JL, Dubner R, Hargreaves KM. Opioid analgesia at peripheral sites: a target for opioids released during stress and inflammation. Anesth Analg 1987;66:1277–81.
2. Stein C, Comisel K, Halmerl E, et al. Analgesic effect of intraarticular morphine after arthroscopic knee surgery. N Engl J Med 1991;325:1123–6.
3. Kalso E, Tramèr MR, Carroll D, et al. Pain relief from intraarticular morphine after knee surgery: a qualitative systemic review. Pain 1997;71:127–34.
4. McQuay H, Moore A, eds. An evidence-based resource for pain relief. Oxford: Oxford University Press, 1998:10–3.
5. Whitford A, Healy M, Joshi GP, et al. The effect of tourniquet release time on the analgesic efficacy of intraarticular morphine after arthroscopic surgery. Anesth Analg 1997;84:791–3.
6. Klinken C. Effects of tourniquet time in knee arthroscopy patients receiving intraarticular morphine combined with bupivacaine. CRNA 1995;6:37–42.
7. Khoury GF, Garland DE, Stein C. Intraarticular opioid-local anesthetic combinations for chronic joint pain. Middle East J Anesthesiol 1994;12:579–85.
8. Likar R, Schafer M, Paulak F, et al. Intraarticular morphine analgesia in chronic pain patients with osteoarthritis. Anesth Analg 1997;84:1313–7.
9. De Andrés J, Bellver J, Barrera L, et al. Comparative study of analgesia after knee surgery with intraarticular bupivacaine, intraarticular morphine, and lumbar plexus block. Anesth Analg 1993;77:727–30.
10. Goranson BD, Lang S, Cassidy JD, et al. A comparison of three regional anaesthesia techniques for outpatient knee arthroscopy. Can J Anaesth 1997;44:371–6.
11. Heard SO, Edwards WT, Ferrari D, et al. Analgesic effect of intraarticular bupivacaine or morphine after arthroscopic knee surgery: a randomized, prospective, double blind study. Anesth Analg 1992;74:822–6.
12. Raja SN, Dickstein RE, Johnson CA. Comparison of analgesic effects of intraarticular bupivacaine and morphine following arthroscopic knee surgery. Anesthesiology 1992;77:1143–7.
13. Gupta A, Axelsson K, Allvin R, et al. Postoperative pain following knee arthroscopy: the effects of intra-articular ketorolac and/or morphine. Reg Anesth Pain Med 1999;24:225–30.
14. Reuben SC, Connelly NR. Postarthroscopic meniscus repair analgesia with intraarticular ketorolac or morphine. Anesth Analg 1996;82:1036–9.
15. Welch BL. The significance of the difference between two means when the population variances are unequal. Biometrika 1937; 29:350–62.
16. Grizzle JE, Starmer CF, Koch GG. Analysis of categorical data by linear models. Biometrics 1969;25:489–504.
17. Greenland S. Meta-analysis. In: Rothman KJ, Greenland S, eds. Meta-analysis in modern epidemiology. 2nd ed. Philadelphia: Lippincott-Raven, 1998;643–73.
18. SPSS statistical software. Version 9. Chicago: SPSS Inc, 1998.
19. Joshi GP, McCarroll SM, Brady OH, et al. Intra-articular morphine for pain relief after anterior cruciate ligament repair. Br J Anaesth 1993;70:87–8.
20. Joshi GP, McSwiney M, Hurson BJ, et al. Effect of intraarticular morphine on analgesic requirements after anterior cruciate ligament repair. Reg Anesth 1993;18:254–7.
21. Lyons B, Lohan D, Flynn CG, et al. Intra-articular analgesia for arthroscopic meniscectomy. Br J Anaesth 1995;75:552–5.
22. Haynes TK, Appadurai IR, Power I, et al. Intra-articular morphine and bupivacaine analgesia after arthroscopic knee surgery. Anaesthesia 1994;49:54–6.
23. Cepeda MS, Uribe C, Betancourt J, et al. Pain relief after knee arthroscopy: intra-articular morphine, intra-articular bupivacaine or subcutaneous morphine? Reg Anesth 1997;22:233–8.
24. Kanback M, Akpolat N, Öcal T, et al. Intraarticular morphine administration provides pain relief after knee arthroscopy. Eur J Anaesthesiol 1997;14:153–6.
25. Joshi GP, MacCarroll SM, O'Brien TM, et al. Intraarticular analgesia following knee arthroscopy. Anesth Analg 1993;76: 333–6.
26. Dalsgaard J, Felsby S, Juelsgaard P, et al. Low-dose intraarticular morphine analgesia in day case knee arthroscopy: a randomized double-blind prospective study. Pain 1994;56: 151–4.
27. Jaureguito JW, Wilcox JF, Cohn SJ, et al. A comparison of intraarticular morphine and bupivacaine for pain control after outpatient knee arthroscopy: a randomized, double-blind study. Am J Sports Med 1995;23:350–3.
28. Joshi GP, McCarroll SM, Cooney CM, et al. Intra-articular morphine for pain relief after knee arthroscopy. J Bone Joint Surg Br 1992;74:749–51.
29. Richardson MD, Bjorksten AR, Hart JAL, McCullough K. The efficacy of intra-articular morphine for postoperative knee arthroscopy analgesia. Arthroscopy 1997;13:584–9.
30. Chan ST. Intraarticular morphine and bupivacaine for pain relief after therapeutic arthroscopic knee surgery. Singapore Med J 1995;36:35–7.
31. Karlsson J, Rydgren B, Eriksson B, et al. Postoperative analgesic effects of intra-articular bupivacaine and morphine after arthroscopic cruciate ligament surgery. Knee Surg Sports Traumatol Arthrosc 1995;3:55–9.
32. Dierking GW, Östergaard HT, Dissing CK, et al. Analgesic effects of intra-articular morphine after arthroscopic meniscectomy. Anaesthesia 1994;49:627–9.
33. De Andes J, Valia JC, Barrera L, Colomina R. Intra-articular analgesia after arthroscopic knee surgery: comparison of three different regimens. Eur J Anaesthesiol 1998;15:10–5.
34. Wrench IJ, Taylor P, Hobbs GJ. Lack of efficacy of intra-articular opioids for analgesia after day-case arthroscopy. Anaesthesia 1996;51:920–2.
35. Söderlund A, Westman L, Ersmark H, et al. Analgesia following arthroscopy: a comparison of intraarticular morphine, pethidine and fentanyl. Acta Anaesthesiol Scand 1997;41:6–11.
36. Aasbo J, Raeder JC, Grogaard B, Roise O. No additional analgesic effect of intra-articular morphine or bupivacaine compared with placebo after elective knee arthroscopy. Acta Anaesthesiol Scand 1996;40:585–8.
37. Ruwe PA, Klien I, Shields CL. The effect of intraarticular injection of morphine and bupivacaine on postarthroscopic pain control. Am J Sports Med 1995;23:59–64.
38. Gatt CJ, Parker RD, Tetzlaff JE, et al. Preemptive analgesia: its role and efficacy in anterior cruciate ligament reconstruction. Am J Sports Med 1998;26:524–9.
39. Hege-Scheuing G, Michaelsen K, Buhler A, et al. Analgesie durch intraartikulares Morphin nach Kniegelenks-arthroskopien? Eine doppelblinde, randomisierte Studie mit patientenkontrollierter Analgesie. Anaesthesist 1995;44:351–8.
40. Laurent SC, Nolan JP, Pozo JL, Jones CJ. Addition of morphine to intra-articular bupivacaine does not improve analgesia after day case arthroscopy. Br J Anaesth 1994;72:170–3.
41. Björnsson A, Gupta A, Vegfors M, et al. Intraarticular morphine for postoperative analgesia following knee arthroscopy. Reg Anesth 1994;19:104–8.

42. Rosseland LA, Stubhaug A, Skoglund A, Breivik H. Intra-articular morphine for pain relief after knee arthroscopy. Acta Anaesthesiol Scand 1999;43:252–7.
43. Tetzlaff JE, Dilger JA, Abate J, Parker RD. Postoperative intra-articular morphine and bupivacaine for pain control after outpatient arthroscopic anterior cruciate ligament reconstruction. Reg Anesth Pain Med 1999;24:220–4.
44. Likar R, Kapral S, Steinkellner H, et al. Dose-dependency of intra-articular morphine analgesia. Br J Anaesth 1999;83:241–4.
45. Fisher DM. Research design and statistics in anesthesia. In: Miller RD, ed. Anesthesia. 5th ed. Philadelphia: Churchill Livingstone, 2000:758–9.
46. Möiniche A, Mikkelsen S, Wetterslev J, Dahl JB. A systematic review of intra-articular local anesthesia for postoperative pain relief after arthroscopic knee surgery. Reg Anesth Pain Med 1999;24:430–7.
47. Stein C. The control of pain in peripheral tissue by opioids. N Engl J Med 1995;332:1685–90.
48. Stein C, Pfluger M, Yassouridis A, et al. No tolerance to peripheral morphine analgesia in presence of opioid expression in inflamed synovia. J Clin Invest 1996;98:793–9.