A systematic review of the peripheral analgesic effects of intraarticular morphine
Gupta A, Bodin L, Holmstrom B, Berggren L

Authors' objectives
The authors state that the primary aim of this systematic review was to establish whether morphine injected intra-articularly 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.

Searching
MEDLINE was searched between 1986 and 2000 for original publications, review articles, abstracts, case reports and letters to the editor. The keywords used were 'opiate/opioids', 'morphine', 'arthicular', 'arthroscopy', 'analgesia', 'pain' and 'postoperative'. In addition, the Cochrane Library, EMBASE, and the reference lists of all articles, review articles and published systematic reviews, were searched. No attempt was made to obtain access to unpublished studies.

Study selection
Study designs of evaluations included in the review
Only randomised and prospective studies were included in the review. The included studies were randomised, controlled double-blinded trials.

Specific interventions included in the review
Studies in which a direct comparison was made between morphine and placebo injected intra-articularly were included in the review. Only those studies in which morphine was injected into the knee joint were included.

Studies were excluded if: (1) the primary aim was to assess the effect of tourniquet time on post-operative analgesia; (2) the primary aim was to assess the effects of intra-articular morphine on chronic pain; or (3) they compared regional nerve blocks with intra-articular analgesics for post-operative pain relief.

Studies included in the review were of general, regional, local or epidural anaesthesia. The morphine doses used were between 1 and 10 mg, and studies with and without tourniquet use were included. The duration of post-operative observation in the included studies ranged from 2 to 72 hours.

Participants included in the review
Only studies of humans (volunteers and patients) were included. The studies included in the review were of patients undergoing knee arthroscopy or anterior cruciate ligament repair.

Outcomes assessed in the review
The authors do not specify any inclusion or exclusion criteria relating to the outcomes.

Two measures of pain relief were used in the included studies. The first was a direct measure, the visual analogue score (VAS) at rest, where the score ranged from 0 for no pain to 10 for worst imaginable pain. The second was an indirect measure, the total consumption of analgesics after surgery. These were measured during the early (0 to 2 hours), intermediate (2 to 6 hours), and late (6 to 24 hours) phases post-operatively (phases I, II and III, respectively).

How were decisions on the relevance of primary studies made?
Three of the authors reviewed the articles for relevance on the basis of the inclusion and exclusion criteria.

Assessment of study quality
The quality of the included studies was assessed on the basis of criteria recommended by McQuay and Moore (see Other Publications of Related Interest no.1). The authors do not state how the papers were assessed for quality, or how many of the reviewers performed the quality assessment.
**Data extraction**
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

Data were extracted from the included primary studies on the patient numbers, type of operation, type of anaesthesia, presence or absence of tourniquet, dose of morphine, duration of post-operative observation, and results. Where the VAS was presented in figures only, two authors independently assessed the VAS.

**Methods of synthesis**
**How were the studies combined?**
The studies were combined in a meta-analysis, using a random-effects model (see Other Publications of Related Interest no.2) in which the studies were weighted by the inverse variance (see Other Publications of Related Interest no.3).

**How were differences between studies investigated?**
The essential homogeneity assumption was tested using the chi-squared test (see Other Publications of Related Interest no.3).

**Results of the review**
Twenty-seven articles were included in the review. The total number of study participants was unclear; it was reported as 1,748 in the text of the article but, from the data presented, it is apparently 1,848.

Nineteen articles were identified in which the data were presented in a way that could be used in a meta-analysis.

There was a mean reduction in the pain intensity in the morphine group, compared with the placebo, during each of the three post-operative phases. The mean reduction was 11.6 mm (95% confidence interval, CI: 6.6, 16.6), 17.0 mm (95% CI: 11.7, 22.3) and 14.7 mm (95% CI: 9.2, 20.2) during phases I, II and III, respectively, when all 19 studies were included in the analysis. Of the 13 studies in which beneficial effects of morphine were found, 6 found significantly less analgesic consumption in the morphine group, 6 found no significant difference between the groups, and one stated differences in analgesic consumption but did not refer to statistical significance.

A subgroup analysis was conducted to determine whether the study quality affected heterogeneity or the difference between the placebo and treatment groups. Study homogeneity was present only when the quality scores were equal to or greater than four, and only for the early and intermediate post-operative phases. For the intermediate phase, the treatment effect, though still positive, was smaller than when all the studies were included.

No clear dose-response effect was seen when the VAS was used as a measure of pain, but it was seen in one study when the 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.

**Authors' conclusions**
The meta-analysis of the studies available in the literature has shown that morphine injected into the intra-articular 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.

**CRD commentary**
The review question was clearly defined in terms of the primary and secondary outcomes, and the inclusion and exclusion criteria were specified. The search of the published literature was comprehensive. However, no attempt was made to identify unpublished studies, and as no assessment of publication bias was made its presence cannot be ruled out.
The authors stated that the quality of the included studies was assessed and a quality score was reported, but no detail of the scale used or its method of application were provided. The results of the quality assessment were not used to either exclude studies of low quality or to give differential weight to those studies included in the analysis. It is, therefore, difficult to assess the possible impact of any methodological flaws in the included primary studies on the overall outcome of the meta-analysis presented.

The details of the individual studies included in the review were clearly presented. However, no details on the study participants were reported, other than their surgical procedure. It is, therefore, difficult to assess the degree to which the findings of this review might be applicable to the general population of patients undergoing knee surgery.

The statistical analysis was appropriate and rigorously conducted.

The authors’ conclusions follow from their results as reported.

**Implications of the review for practice and research**

Practice: The authors did not state any implications for practice.

Research: The authors state that 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.

**Bibliographic details**


**PubMedID**

11524353

**Original Paper URL**

http://www.anesthesia-analgesia.org

**Other publications of related interest**


**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Analgesics, Opioid /administration & dosage /pharmacology; Dose-Response Relationship, Drug; Humans; Injections, Intra-Articular; Morphine /administration & dosage /pharmacology; Pain Measurement; Pain, Postoperative /drug therapy; Peripheral Nervous System /drug effects; Prospective Studies; Randomized Controlled Trials as Topic

**AccessionNumber**

12001002127

**Date bibliographic record published**

28/02/2003

**Date abstract record published**
Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.