Peripheral opioids: a systematic review of intra-articular morphine

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Authors' objectives
To assess the analgesic effect of intra-articular morphine.

Searching
MEDLINE (from 1966 to September 1998), EMBASE and the Oxford Pain Relief Database (1950 to 1994) were searched for reports in any language. The search terms included ‘intra-articular’, ‘opiates’, ‘opioids’, ‘morphine’ and ‘random’. The reference lists of the retrieved reports and review articles were examined. Unpublished reports, abstracts and reviews were not included.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with ten or more patients per treatment group were eligible.

Specific interventions included in the review
Studies that compared intra-articular morphine with placebo (saline) or different doses of intra-articular morphine, or compared intra-articular morphine with systemic (intravenous, intramuscular, or subcutaneous) morphine were eligible. Direct comparisons of intra-articular morphine and local anaesthetic agents were excluded, as were reports on pethidine and fentanyl. The dose of intra-articular morphine ranged from 0.5 to 10 mg. The control interventions were intra-articular bupivacaine (0.25 to 0.5%), intra-articular saline, and intravenous, intramuscular and subcutaneous morphine (1 to 10 mg).

Participants included in the review
Studies of patients undergoing general anaesthesia were eligible. Studies of patients undergoing spinal or epidural anaesthesia, or infiltrations of local anaesthetic into joints, were excluded. All participants had undergone knee surgery including arthroscopic day surgery.

Outcomes assessed in the review
Studies that used standardised methods for measuring pain intensity were eligible. Pain intensity was assessed using visual analogue scales for two time periods: early, defined as up to 6 hours after intra-articular injection; and late, defined as from 6 to 24 hours after injection. Effectiveness was defined as a significant difference between the active and the control in pain intensity (early or late) or in total consumption of rescue analgesics. Adverse effects were also assessed. The demonstration of an analgesic effect of morphine required that the internal sensitivity had to be derived from the following: a statistically-significant difference between a known analgesic (intra-articular local anaesthetic) and placebo or intra-articular morphine different from placebo; dose-response for intra-articular morphine; or a statistically-significant difference between intra-articular morphine and the same dose of morphine given systemically.

How were decisions on the relevance of primary studies made?
Two reviewers independently read each report that could possibly be described as an RCT and scored it for inclusion using the 3-item validity scale. Consensus was then reached.

Assessment of study quality
Validity was assessed and scored using the 3-item scale described by Jadad et al, which assesses proper randomisation, double-blinding, and the reporting of drop-outs and withdrawals (see Other Publications of Related Interest). Two reviewers independently scored each report according to the validity criteria and then reached consensus.

Data extraction
The author does not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

The following data were extracted: information about the treatments and controls; the types of surgery and anaesthesia; the number of patients enrolled and analysed; study design; observation periods; and outcome measures.

**Methods of synthesis**

How were the studies combined?
The studies were grouped according to whether they demonstrated internal sensitivity, and a narrative synthesis was undertaken.

How were differences between studies investigated?
Differences between the studies, in relation to internal sensitivity and morphine dose, were discussed in the text of the review.

**Results of the review**

Forty-five RCTs (2,400 patients) were included.

The following were inadequately described in the primary studies: the randomisation method, concealment of treatment allocation, blinding, and description of withdrawals and drop-outs. The method of randomisation was described in 7 RCTs. In many RCTs it was unclear who was blinded. Patients were instructed in the use of visual analogue scales in a minority of the studies, and most patients were sent home with a questionnaire 2 to 6 hours after surgery. Non-standardised measures were used to record the consumption of supplementary analgesia.

Morphine versus saline in studies where bupivacaine was used as an active control (9 RCTs).

Six RCTs were sensitive, as defined by a significant analgesia effect of bupivacaine compared with saline. All 6 RCTs found a significant effect on pain for intra-articular morphine versus placebo at either early or late times.

Early effect (4 RCTs): one of the 4 RCTs using 1 mg intra-articular morphine found an early effect on pain. Other RCTs that found an early effect on pain used 5 or 10 mg intra-articular morphine.

Late effect (5 sensitive RCTs): all 5 RCTs found a significant effect on pain for intra-articular morphine versus saline.

Analgesic consumption at 24 to 48 hours (4 sensitive RCTs): 3 of the 4 RCTs found significantly lower analgesic consumption for morphine versus saline.

Morphine versus saline with no active bupivacaine control (8 RCTs). Four of the 8 RCTs found significantly lower visual analogue pain scores for intra-articular morphine versus saline in the early period.

Intra-articular morphine versus systemic morphine control (6 RCTs: 3 RCTs used intravenous morphine, 2 RCTs used intramuscular morphine, and one RCT used subcutaneous morphine). Late period: no RCT found any significant difference between intra-articular and systemic morphine for pain.

Total analgesic consumption (4 RCTs): one RCT found significantly reduced analgesic consumption for 1 mg intra-articular morphine versus 1 mg intravenous morphine. Combination of intra-articular morphine and bupivacaine versus intra-articular saline (10 studies of which 8 also included a control group with a combination of intra-articular morphine plus bupivacaine).

Four of the 6 studies that were sensitive to bupivacaine alone, and showed a positive effect for morphine, also showed a significant effect for the combined treatments in the early period. All 5 studies analysed for the late period showed a positive effect for the combination.

Dose-response (5 RCTs using intra-articular morphine alone).
None of the studies had evidence of internal sensitivity. The RCTs found no consistent dose-response effect.

Adverse effects.

Only one adverse effect attributed to intra-articular morphine (1 mg) was reported (pruritus in 1 patient). The effect of intra-articular injections on the knee was not mentioned.

**Authors' conclusions**

Intra-articular morphine may have some effect in reducing post-operative pain intensity and the consumption of analgesia. These studies had significant problems in their design, data collection, statistical analysis and reporting.

**CRD commentary**

The aims were stated, and the inclusion criteria were defined in terms of the intervention, study design, participants and outcome. Several relevant sources were searched, no language restrictions were applied, and the methods used to select the studies were described. The lack of an attempt to locate unpublished material may have resulted in the omission of other relevant studies. Validity was formally assessed using validated criteria, methodological flaws in the included studies were discussed in the text of the review, and the methods used to assess validity were described. Relevant data were extracted and tabulated, but the methods used to extract the data were not described. The studies were grouped according to a defined sensitivity index and, appropriately, a narrative synthesis was undertaken. Unfortunately, it was not always clear how many studies had assessed specific outcomes, and this hampered the interpretation of the results.

The effect of morphine dose on the results was highlighted in the summary. The evidence presented supports the author's conclusions.

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

Practice: The author states that the evidence for intra-articular morphine is not compelling and that, at present, it should be used as a basis for future research rather than in clinical practice.

Research: The authors state that trials of better methodological quality are needed for a conclusive answer that intra-articular morphine is analgesic, and that any analgesia produced is clinically useful. They also state that well-controlled follow-up studies should investigate whether intra-articular morphine has any long-term effects.

**Bibliographic details**


**Other publications of related interest**


**Indexing Status**

Subject indexing assigned by CRD

**MeSH**

Analgesics, Opioid /therapeutic use; Injections, Intra-Articular; Pain, Postoperative /prevention & control

**AccessionNumber**

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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.