No pain, no gain: clinical excellence and scientific rigour: lessons learned from IA morphine

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Authors' objectives
To include all evaluable studies on intra-articular morphine, to set simple criteria for study sensitivity, to analyse factors that can render studies insensitive, and to analyse the effectiveness of intra-articular morphine.

Searching
MEDLINE (from 1966 to March 2000), EMBASE (from 1980 to March 2000), the Cochrane Library (Issue 3, 2000) and the Oxford Pain Relief Database (from 1950 to 1994) were searched. There was no restriction on the language of publication. The search terms were not reported. The reference lists of retrieved articles and reviews were examined for additional trials. Abstracts, review articles and unpublished reports were not considered and authors were not contacted for original data.

Study selection
Study designs of evaluations included in the review
Only double-blind randomised controlled trials (RCTs) comparing intra-articular morphine with placebo (normal saline) were included in the review. The RCTs had to have at least 10 patients in each study arm.

Specific interventions included in the review
Studies were included if they evaluated intra-articular morphine against placebo (normal saline). In the included trials, morphine was administered at doses of 1, 2, 3, 4, 5 or 10 mg.

Participants included in the review
The participants were adults receiving intra-articular morphine to the knee joint only.

Outcomes assessed in the review
Studies were included if they reported pain intensity outcomes using a visual analogue scale (VAS) or a 4-point pain intensity categorical scale or analgesic consumption with patient-controlled analgesia (PCA).

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Each RCT was scored for quality and validity using a 3-item quality scale (see Other Publications of Related Interest 1) and a 5-item validity scale (see Other Publications of Related Interest 2). The authors did not state how the papers were assessed for validity, or how many reviewers performed the validity assessment.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data were extracted on the treatment and control groups, anaesthesia, surgery, number of patients randomised and analysed, consumption of supplemental analgesics, mean VAS for pain intensity (VASpi) scores and level of significance.

Methods of synthesis
How were the studies combined?
Three periods were defined for the evaluation of effectiveness: immediate (0 to 2 hours), early (2 to 6 hours) and late (6 to 30 hours). Effectiveness was defined as a statistically-significant difference (as reported in the original trials) between morphine and normal saline. For each outcome period, a study was judged to be sensitive (i.e. able to detect differences between the treatment arms) if the mean VASpi-value was above 30/100 in the control group.

The number of 'positive' and 'negative' (non significant) results were reported for 'sensitive' and 'insensitive' trials.
These were presented as part of a narrative synthesis, which was grouped by comparison type (e.g. intra-articular morphine versus placebo, dose-response, cross-route comparison).

How were differences between studies investigated?
'Sensitive' and 'insensitive' trials were compared on multiple factors thought to be associated with the reduction of post-operative pain. No other sources of heterogeneity were explicitly explored.

Results of the review
Twenty-five publications reporting on 28 RCTs were included.

The quality scale ratings ranged from 2 to 5 (median 3; 15 of the 25 comparisons had scores of at least 3) and the validity scores ranged from 2 to 11 (median 8).

Sensitive trials
Intra-articular morphine versus placebo, immediate period (0 to 2 hours): Fifteen comparisons were sensitive (7 positive, 8 negative). Of the eight negative comparisons, seven were of 1mg and one of 4mg. Of the seven positive comparisons, one was of 1mg, one of 3mg and five were of 5mg.

Intra-articular morphine versus placebo, early period (2 to 6 hours): Twelve comparisons were sensitive (8 positive, 4 negative). Of the four negative comparisons, three were of 1mg and one of 4mg. Of the eight positive comparisons, two were of 1mg, one of 3mg and five were of 5mg.

Intra-articular morphine versus placebo, late period (6 to 30 hours): Thirteen comparisons were sensitive (10 positive, 3 negative). All three negative comparisons were of 1mg. Of the ten positive comparisons, four were of 1mg, one of 3mg, one of 4mg and four of 5mg.

Intra-articular morphine versus placebo, PCA outcome trials: Two comparisons were sensitive. In both studies, statistically more PCA morphine was used in the placebo groups than in the intra-articular morphine (2mg and 5mg) groups.

Dose-response trials: One comparison was sensitive; 5mg intra-articular morphine was shown to be statistically superior to 1mg intra-articular morphine.

Cross-route comparison: One cointertrial comparison was sensitive for immediate and late outcomes; no statistical difference was shown between 5mg of intra-articular morphine and 5mg intramuscular morphine.

Insensitive trials
Immediate period (0 to 2 hours): All 10 insensitive trials were negative.

Early period (2 to 6 hours): Nine of the 10 insensitive trials were negative.

Late period (6 to 30 hours): Ten of the 11 insensitive trials were negative.

Dose-response: None of the three dose response comparisons showed a difference between the groups.

Cross-route comparisons; none of the two comparisons showed a difference between intra-articular and intramuscular administration, or intra-articular and subcutaneous administration.

Authors’ conclusions
Intra-articular morphine at a dose of 5mg seemed to provide relief of post-operative pain for up to 24 hours. This would be of clinical benefit in a group of patients who are sent home after an arthroscopic procedure. The real significance of this pre-emptive treatment still remains obscure, as most of the patients were given various analgesics and the pain intensity levels reflected the effect of both measures. Adverse events were not rigorously reported and no
conclusions could be drawn about the total benefit of intra-articular morphine after arthroscopic day-case surgery.

**CRD commentary**

The review was based on a well-defined question, supported by appropriate inclusion or exclusion criteria. In addition to searching electronic databases, the authors attempted to identify studies from other sources such as reference lists. No language restrictions were imposed, but the exclusion of unpublished reports could have introduced publication bias. Each study was given separate validity and quality scores, though these do not appear to have had any influence in the synthesis or interpretation of results. Some details of the included studies were provided in the review, but these were limited. It was unclear how many reviewers were involved in any of the selection, validity assessment or data extraction procedures.

The included studies were combined using a 'vote-count' approach, where the number or proportion of statistically-significant results are counted for each section of interest. This approach is open to criticism since it gives no indication of the magnitude of any effect, and it may discount the findings of valid studies that are insufficiently powered to detect a statistically-significant effect. Although the authors justified separating 'sensitive' and 'insensitive' studies, their findings might be considered more robust if the arbitrary cut-off for trial sensitivity had been varied in a sensitivity analysis. The authors' conclusions appear to follow from the evidence as presented, but the above caveats should be borne in mind when interpreting these conclusions.

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

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

**Research:** The authors stated that future studies could increase sensitivity by measuring pain during movement. Where PCA consumption is not used, time to rescue medication would be a useful outcome. This could show whether intra-articular morphine is of clinical relevance and of statistical significance.

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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.