Analgesic efficacy of peripheral opioids (all except intra-articular): a qualitative systematic review of randomised controlled trials

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Authors' objectives
To test the evidence that peripheral opioids (all except intra-articular) improve the quality of either intra-operative regional anaesthesia or post-operative analgesia.

Searching
MEDLINE from 1966 to September 1996, EMBASE from 1981 to 1996, and the Oxford Pain Relief Database from 1950 to 1994, were searched for studies reported in any language. A number of different search strategies were employed. Additional reports were identified from the reference lists of the retrieved reports and from review articles. Unpublished reports and abstracts were not considered. The authors of the primary studies were not contacted for original data.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) which met the following inclusion criteria: at least 10 patients per treatment group; any opioid except pethidine; any peripheral site of injection except intra-articular; and standardised methods of measuring sensory block and pain intensity.

Specific interventions included in the review
Peripheral opioids compared with either local anaesthetics, placebo (saline), no treatment or an opioid given by a different route. The peripheral opioids included morphine, fentanyl, alfentanil, buprenorphine and butorphanol. Reports of intra-articular opioids and of pethidine were excluded.

Participants included in the review
Healthy volunteers were used in experimental pain trials (4 studies). The remaining participants were patients in a variety of surgical settings with the following: intravenous regional anaesthesia (Bier's block); intrapleural, intraperitoneal, incisional, and dental injections; perineural blocks (femoral, ankle block, intercostal); and brachial plexus sheath injections (axillary, supraclavicular and interscalene approaches). No further details of the participants (e.g. age and gender) were reported.

Outcomes assessed in the review
The outcomes assessed were: intra-operative efficacy, i.e. onset and quality (loss of pinprick and touch sensation) and duration of sensory block; and post-operative efficacy (pain intensity, delay until first analgesic, analgesic consumption). Pain intensity measurement, where reported, was analysed using a visual analogue scale or a verbal rating scale.

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

Assessment of study quality
The 3-item, 5-score quality scale of Jadad et al. (see Other Publications of Related Interest) was used to assess validity. Each of the four authors read and quality-scored each report independently. Consensus was then achieved.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the date extraction. However, data showing any statistically-significant difference (p<0.05) between the opioid and control, as indicated in the original report, were extracted. The authors then met to achieve consensus (vote counting procedure) on whether such a statistically-significant difference was of clinical relevance. The authors' decision on clinical relevance was then compared with the original authors' conclusion of efficacy.

**Methods of synthesis**
How were the studies combined?
A narrative synthesis was undertaken.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

**Results of the review**
Twenty-six RCTs (published in 25 reports) were included. Of the 952 patients, 485 received an opioid.

The average size was 15 patients per group (range: 10 to 32). The median quality score was 2 out of a possible 5 (range: 1 to 4). There was a relationship between the quality scores of the reports and the original authors' conclusions on the efficacy of peripheral opioids. The quality scores of the 10 trials which reported positive estimates of efficacy were 2 or below. Seven of the 16 remaining trials (2 experimental and 14 clinical) that had negative conclusions had a quality score of 3 or 4.

The results of the experimental pain trials were not taken into account when estimating the overall efficacy of peripheral opioids.

Bier's block (4 trials).

Fentanyl was used in 2 trials, one of which did not show any significant difference between fentanyl plus local anaesthetic and local anaesthetic alone. The other trial reported significantly improved quality of the sensory block after 15 minutes with 200 microg fentanyl, compared with either saline or 100 microg fentanyl, but concluded that this was not clinically relevant. Morphine was used in 2 trials; in one there was no significant difference between morphine and saline, while in the other both onset of, and recovery from anaesthesia and analgesia were significantly better compared with local anaesthetic alone. However, the review's authors concluded these differences were not clinically relevant.

Other peripheral sites (5 trials).

All 5 trials used morphine. Four did not show any difference between morphine and control during the post-operative period when applied into a tooth socket, a surgical wound, or by intraperitoneal or intrapleural block. The fifth trial reported a statistically-significant improvement in verbal pain rating scores, which were lower for 20 hours, with 20 mg morphine given intrapleurally compared with the same drug and dose given intravenously. The review's authors considered the outcome to be of little clinical relevance due to the atypically high dose used.

Perineural (3 trials).

No trials reported any significant difference between the opioid and the control.

Brachial plexus (10 trials).

In 3 trials, morphine was combined with a local anaesthetic and applied by an axillary or interscalene route. The comparators were systemic morphine or axillary saline. No improvement was demonstrated in 2 of the 3 trials. The third trial (axillary route) reported similar pain scores in the groups, but significantly lower post-operative analgesic consumption with the opioid. However, the review's authors did not consider this difference clinically important in this acute setting.
Four trials combined fentanyl with a local anaesthetic and compared it with a local anaesthetic alone or with another route of injection. Two reported a significant improvement with fentanyl, one of which was considered by the trial’s authors to be clinically relevant since the speed of onset of sensory block with fentanyl was 5 minutes faster.

Alfentanil added to a local anaesthetic led to a significant improvement in the duration of sensory and motor block after surgery, compared with local anaesthetic plus placebo.

Butorphanol perfusion into the plexus sheath led to significantly lower visual analogue scale scores for pain intensity up to 24 hours, compared with the same drug given intravenously.

Buprenorphine 3 microg/kg was compared with morphine 50 microg/kg; both were added to local anaesthetic before supraclavicular injection. The duration and quality of post-operative analgesia were significantly better with buprenorphine.

No adverse effects attributable to the route of administration were reported.

**Authors’ conclusions**
Five of the 10 clinical trials measuring intra-operative efficacy reported statistically-significant efficacy with opioids compared with control; however, none were judged to be clinically relevant. Five of the 17 clinical trials measuring post-operative efficacy reported a significant difference in favour of the opioid; however, none were judged to be clinically relevant. Trials of lower quality were more likely to report increased efficacy with opioids. Adverse events related to the route of administration were not reported. These trials provided no evidence for a clinically relevant peripheral analgesic efficacy of opioids in acute pain.

**CRD commentary**
This review was a useful summary of the evidence for analgesic efficacy of peripheral opioids in acute pain. The literature search was fairly comprehensive with no language restrictions. A common quality scale was used, and it is interesting to note that studies which reported positive results had a lower quality score in general. The retrieved studies covered many different types of surgery, routes of administration and drugs, and used different comparators. The authors were therefore correct in not attempting a quantitative pooling of the data. The narrative review was reasonably clear and intelligent, and the authors stated whether they considered the conclusions of each trial to be appropriate. On the whole, this was a good review. In addition, the authors’ conclusions are suitably cautious given the huge variation in the nature of the primary evidence.

**Implications of the review for practice and research**
The authors state that more evidence on the clinical use of peripheral opioids is needed, and that the authors of original reports should curb the tendency to over-interpret their findings and to confuse statistical significance with clinical relevance.

**Funding**
European Union Biomed, grant number BMH4 CT95 0172; NHS Research and Development Health Technology Assessment Programme 94/11/4; UPSA France; UK ORS award.

**Bibliographic details**

**PubMedID**
9313271
Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Analgesics, Opioid /administration & dosage /therapeutic use; Humans; Intraoperative Period; Postoperative Care; Randomized Controlled Trials as Topic; Treatment Outcome

AccessionNumber
11997001151

Date bibliographic record published
31/10/1999

Date abstract record published
31/10/1999

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.