Nefopam for the prevention of postoperative pain: quantitative systematic review
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CRD summary
The authors concluded that there was limited evidence that the non-opioid analgesic nefopam may be useful for the prevention of postoperative pain in surgical patients, but that further research was required. There were limitations to the review, but overall the authors’ cautious conclusions reflect limited evidence from diverse trials.

Authors' objectives
To evaluate the analgesic efficacy and adverse effects of nefopam used for the relief of postoperative pain.

Searching
MEDLINE, EMBASE, the Cochrane Library, WHOLIS (World Health Organization library database), the African Index Medicus and LILACS (Latin American and Caribbean Health Sciences Literature) were searched to January 2008. Search terms were reported. No language restrictions were applied. In addition, reference lists of retrieved studies were screened. Studies reported as abstracts were excluded.

Study selection
Randomised controlled trials (RCTs) that compared nefopam with an inactive control (placebo or no treatment) for the prevention of postoperative pain were eligible for inclusion. Trials had to assess pain outcomes or adverse effects. Trials of healthy volunteers and trials with fewer than 10 patients per treatment group were excluded. The review assessed pain intensity at rest and on movement or during coughing, and cumulative postoperative morphine consumption.

The included trials evaluated a variety of different nefopam treatment regimens including continuous intravenous infusion, single and repeat intravenous injection, single and repeat intramuscular injection and single oral dose. Cumulative doses ranged from 20mg to 160mg for intravenous regimens, from 45mg to 90mg for oral regimens, and from 20mg to 100mg for intramuscular regimens. Trials reported a variety of pain measures at various times post-operatively (from 60 minutes to 48 hours). Patients were adults undergoing a variety of surgical procedures including: major abdominal surgery; episiotomy; hip arthroplasty; gynaecological and orthopaedic surgery; and dental extraction.

The authors did not state how papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Validity was assessed using a modified four-item seven-point Oxford scale that evaluated randomisation, allocation concealment, blinding and description of withdrawals.

One reviewer assessed validity and this was independently checked by two other reviewers. Discrepancies were resolved by discussion.

Data extraction
Continuous outcomes were extracted as means and standard deviations or standard errors; authors were contacted for missing data. Where required, data were extracted from graphs. Zero to 10cm visual analogue scales (VAS) were converted to 0 to 100mm.

One reviewer extracted data and this was independently checked by two other reviewers.

Methods of synthesis
Pooled weighted mean differences (WMD) and relative risks (RR) with 95% confidence intervals (CI) were calculated...
using a fixed-effect model. Where treatment differences were statistically significant, the number-needed-to-treat/number-needed-to-harm (NNT/NNH) with 95% confidence intervals was calculated. Heterogeneity was assessed using the $X^2$ and $I^2$ statistics.

**Results of the review**

Nine RCTs were included (n=359 patients who received nefopam and n=352 patients who received an inactive control). The median quality score was 4 points (range 1 to 7). Three trials scored 2 points for randomisation, five trials scored 1 point for allocation concealment, two trials scored 2 points for blinding and eight trials scored 2 points for follow-up.

**Pain outcomes:** Compared with no treatment or placebo, nefopam was associated with a statistically significant reduction in cumulative 24 hour morphine consumption (WMD -13mg, 95% CI -17.9 to -8.15; n=306 patients; three RCTs), a significant reduction in average pain intensity (WMD -11.5mm, 95% CI -15.1 to -7.85; n=319 patients; three RCTs) and a significant reduction in pain intensity on coughing at 24 hours (45 versus 60mm on 0 to 100mm VAS scale, p value not reported; n=77 patients; one RCT). Heterogeneity was found for 24 hour morphine consumption ($I^2=64.8\%$) but not for pain intensity ($I^2=0\%$).

**Adverse effects:** Compared with no treatment or placebo, nefopam was associated with a statistically significant increase in tachycardia (RR 3.12, 95% CI 1.11 to 8.79; NNH 7; two RCTs) and sweating (RR 4.92, 95% CI 2.0 to 12.1; NNH 13; seven RCTs). There were no significant differences between nefopam and control for other adverse effects.

Results were also reported for nefopam versus active agents from the five included trials that had an active comparator. These results may not represent all available data for nefopam versus active comparators.

**Authors' conclusions**

There was limited evidence that nefopam may be a useful non-opioid analgesic in surgical patients but further research is required.

**CRD commentary**

The review question was clearly stated and inclusion criteria were appropriately defined. Several relevant sources were searched and no language restrictions were applied. It was not clear if attempts were made to minimise publication bias. Methods were used to minimise reviewer errors and bias in the assessment of validity and extraction of data, but it was not clear whether similar steps were taken in study selection. Only RCTs were included, validity was assessed and results were reported. Characteristics of the included trials were adequately summarised. Comparable trials were pooled using meta-analyses but these represented a minority of trials; results from other trials were not reported or discussed. Some attempt at a narrative synthesis that accounted for all available information may have added to the evidence base. There were limitations to the review, but overall the authors' cautious conclusions reflect limited evidence from diverse trials.

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

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

**Research:** The authors stated that there is a need for further trials to determine the optimal regimen and adverse effects of nefopam and the effects of nefopam when used in multimodal regimens. Trials should be adequately powered and assess the effect of nefopam on validated measures of pain intensity and pain relief both at rest and during movement and coughing. Studies are also required in other groups of patients including children.

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