Opioids added to local anesthetics for single-shot intrathecal anesthesia in patients undergoing minor surgery: a meta-analysis of randomized trials

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CRD summary
This review found that the use of morphine added to intrathecally-administered bupivacaine local anaesthetic was associated with analgesic (pain relief) benefits for minor surgery but increased adverse events. The review was generally well conducted and the authors' conclusions are likely to be reliable.

Authors' objectives
To evaluate the effectiveness of opioids added to intrathecally-administered local anaesthetic in patients undergoing minor surgery.

Searching
MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), BIOSIS Previews, and CINAHL were searched up to February 2011 with no language restriction; search terms were reported. Bibliographies of retrieved studies were checked for additional references.

Study selection
Randomised controlled trials (RCTs) in which opioids were added to single-dose intrathecally-administered local anaesthetic in patients (aged 18 years or older) who were undergoing minor surgery were eligible for inclusion. Additional inclusion criteria were that the trials had to report pain outcomes and/or treatment-related adverse events. Trials of patients in labour or undergoing caesarean sections or trials of fewer than 10 patients in each treatment group were excluded from the review.

In most of the included trials, the opioids tested were morphine (0.05 to 2mg) or fentanyl (0.01 to 0.05mg); buprenorphine, diamorphine, meperidine, methadone, pentazocine, sufentanil and tramadol were also used in a few trials. The local anaesthetic that was administered intrathecally in most of the trials was bupivacaine (5 to 20mg). Approximately half of the trials were in patients undergoing orthopaedic surgery; gynaecological and urological surgery was also performed.

One reviewer performed the study selection; two additional reviewers checked the studies against the inclusion criteria and a further two reviewers resolved any discrepancies in selection.

Assessment of study quality
Methodological quality was assessed by one reviewer and checked by two reviewers using a modified 4-item, 7-point Oxford scale for randomisation, allocation concealment, use of blinding, and the reporting of drop-outs.

Data extraction
Data were extracted by one reviewer to calculate odds ratios (OR) for binary outcomes and mean differences for continuous outcomes, with 95% confidence intervals (CI) for the estimates. The reviewers contacted trial authors for missing data.

Two reviewers independently checked the data extracted; any discrepancies were resolved through discussion with two further reviewers.

Methods of synthesis
Pooled odds ratios (OR), weighted mean differences (WMD) and 95% confidence intervals were calculated using a fixed-effect model. Statistical heterogeneity was assessed but the reviewers did not state the methods used for this assessment. Where heterogeneity was present, the results were examined for potential sources of heterogeneity and the results were combined using random-effects models. When the results were statistically significant, numbers needed-to-treat (NNT) and numbers-needed-to-harm were calculated using weighted averages of experimental and control event
Results of the review

Sixty-five RCTs (3,338 patients) were included in the review. Sample sizes ranged from 20 to 188 patients. Quality scores ranged from 1 to 7 points out of 7, with a median quality score of 3 points. Double-blinding was reported in 48 trials. Randomisation procedures were described in 24 trials. Ten trials reported concealment of treatment allocation.

Efficacy

There were significant benefits observed with morphine added to intrathecally administered bupivacaine for the reduction in cumulative 24-hour morphine consumption (WMD -12 mg, 95% CI -18 to -5; 0.05 to 1mg morphine; seven trials), reduction in the proportion of patients requiring postoperative opioids (OR 0.05, 95% CI 0.02 to 0.14; six trials; NNT 2.9, 95% CI 1.5 to 25), and an increased duration of postoperative analgesia (WMD 503 minutes, 95% CI 315 to 641 minutes; 0.05 to 2mg of morphine; 13 trials). There were no differences between the intervention and control groups in postoperative pain intensity at 24 hours post-surgery (six trials). Statistically significant heterogeneity was reported for all outcomes. There was no evidence of a dose-response relationship for these outcomes.

The use of fentanyl (0.01 to 0.05mg) added to intrathecally-administered bupivacaine was associated with increased duration of analgesia (WMD 114 minutes, 95% CI 60 to 16; eight trials, with statistical heterogeneity present), but there was insufficient data on the effect of fentanyl on 24-hour morphine consumption, post-operative pain intensity, and the numbers of patients requiring administration of post-operative opioids.

Safety

The use of morphine with intrathecally-administered bupivacaine was associated with higher rates of pruritus (OR 6.92, 95% CI 4.51 to 10.60;17 trials; NNH 4), nausea (OR 1.66, 95% CI 1.05 to 2.64; 10 trials; NNH 9.8), vomiting (OR 1.88, 95% CI 1.20 to 2.9;13 trials; NNH 10), and urinary retention (OR 3.90, 95% CI 1.94 to 7.86; seven trials; NNH 6.5). The risk of respiratory depression was not statistically significantly different between groups. There was no statistically significant heterogeneity observed for these outcomes.

Fentanyl administered with intrathecal bupivacaine was associated with a statistically significant increase in the risk of pruritus (OR 10.8, 95% CI 7.09 to 16.5; 13 trials; NNH 3.3), but there were no significant differences observed with fentanyl on nausea, urinary retention or respiratory depression.

Data on other opioids buprenorphine, diamorphine, hydromorphone, meperidine, methadone, pentazocine, sufentanil, and tramadol were presented in fewer than five trials and were not analysed further in the review.

Authors' conclusions

The use of morphine and fentanyl with intrathecally-administered bupivacaine was associated with benefits in prolonged analgesia, although morphine was associated with increased risk of gastrointestinal adverse events. Morphine was also associated with opioid sparing and a decrease in pain intensity up to 12 hours after surgery.

CRD commentary

The review addressed a clear question. Criteria for the inclusion of studies in the review were clearly defined. Appropriate databases were searched with no language restrictions for relevant studies, although the restriction of the review to published studies meant there was some risk of publication bias. Steps were taken to minimise errors and biases at each stage of the review process.

Methodological quality was assessed and included trials were found to be of medium quality. The authors decision to combine the results in meta-analyses stratified by opioid type appeared to be justified. Appropriate subgroup and sensitivity analyses were undertaken to attempt to identify sources of heterogeneity. The authors acknowledged some of the limitations of the review related to the size of the trials, the potential for publication bias, and the variety of endpoints reported in the trials which may have contributed to the heterogeneity identified in the review.

The review was well conducted and the authors' conclusions based on the evidence are likely to be reliable.
Implications of the review for practice and research

Practice: The authors stated that other opioids apart from morphine and fentanyl should not be used as adjuvants to other intrathecally-administered anaesthetics until further valid data provides evidence of efficacy and lack of neurotoxicity.

Research: The authors stated that research was required to establish minimum effective doses of morphine and fentanyl. In addition, the definition of respiratory depression varied between trials; future trials should clearly define respiratory depression.

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