Nonsteroidal antiinflammatory drugs for postoperative pain management after lumbar spine surgery: a meta-analysis of randomized controlled trials

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CRD summary
This well-conducted review concluded that addition of NSAIDs to opioid analgesics in lumbar spine surgery provided better postoperative pain control and required lower opioid consumption than opioids alone. Adverse effects were not reduced with NSAIDs. The conclusions appear to be supported by the data presented, although studies were significantly heterogeneous and reported adverse effects selectively.

Authors' objectives
To assess the effectiveness and safety of nonsteroidal anti-inflammatory drugs (NSAIDs) in addition to opioid analgesics on perioperative pain management in lumbar spine surgery.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, PsycINFO, AMED and Science Citation Index Expanded databases and Google and Yahoo search engines were searched for relevant studies. Search terms were (roughly) indicated. Search dates were not given. There were no language restrictions. Reference lists of selected studies and grey literature (Scirus and American Library Association websites) were searched.

Study selection
Studies were eligible if they were double-blind randomised controlled trials of NSAIDs given in addition to opioid analgesics for perioperative pain management during lumbar spine surgery. Studies had to report pain scores and opioid consumption. Any types, doses and administration of NSAIDs in combination with opioid analgesics had to be compared to opioids alone. Studies were excluded if they included a local steroid, local anaesthetic technique or nerve block as part of the anaesthesia.

The included trials considered three types of operation: discectomy, laminectomy and spinal fusion. Surgery was performed at one or two levels. Nine types of NSAIDs were included (non-selective NSAIDs ketorolac, ketoprofen, indomethacin, flurbiprofen, lornoxicam and piroxicam; selective COX-2 NSAIDS including celecoxib, rofecoxib and parecoxib). Twelve trials studied multiple dose effectiveness; single doses were used in the other trials. Morphine was used in 11 trials.

The authors did not state how papers were selected for the review.

Assessment of study quality
Two reviewers independently assessed study quality using the modified Oxford Scale of randomisation, allocation concealment, double blinding and patient flow. Minimum score was 3 (low quality) and maximum score was 7 (4 or more was defined as high quality). Cohen's kappa was used to assess inter rater agreement. Any discrepancies were resolved by consensus.

Data extraction
Two reviewers independently extracted data (including adverse events) for the review and resolved any discrepancies by consensus. Authors of included studies were contacted for additional information where necessary.

Pain intensity was reported using the visual analogue scale from zero to 100mm (100mm was maximum pain). Pain results were reported at zero to two hours, four to six hours, 24 hours, 48 hours and 72 hours. Cumulative opioid consumption was reported at zero to two hours, four to six hours, zero to 24 hours, zero to 48 hours and 49 to 72 hours. All other opioid analgesics were converted to morphine equivalents.

Where means and standard deviations were not available directly, standard deviations were calculated using
recommended methods (or requested from the authors).

**Methods of synthesis**

Data were combined in a meta-analysis. Pain results were reported at a range of time points (with corresponding cumulative opioid dose). Continuous data were assessed as weighted mean differences (WMD) with 95% confidence intervals (CI). Heterogeneity was assessed using $I^2$ and $\chi^2$ tests. Where there was no significant heterogeneity, a fixed-effects model was used; a random effects model was used where there was heterogeneity. Any existing heterogeneity was explored in subgroup analyses for different types of NSAIDs, different types of surgery, types of opioids and trial quality. Sensitivity analyses were carried out to test the robustness of data by exclusion of non patient-controlled analgesia (PCA) morphine trials and low-quality trials.

**Results of the review**

Seventeen RCTs were included in the analysis (n=789 adult patients, n=400 on NSAIDs plus opioids and n=389 on opioids alone). Four studies were scored as low quality and the others as high quality (six trials with scores of 6 or 7).

Pain scores were significantly reduced for patients on NSAIDs plus opioids compared against scores in patients on opioids alone at most time points (WMD between -8.92 and -10.45 at different time points; the difference was non-significant at 48 hours. Heterogeneity existed at most time points ($I^2=57\%$ and 97%). Cumulative opioid consumption was lower in patients on NSAIDs plus opioids than in patients on opioids alone (significant for most time periods except 0-48 hours and 49-72 hours; WMD -20.66, 95% CI -32.32 to -9.0 for 0-24 hours); morphine consumption was reduced by 2mg, 7mg, 20mg and 8mg at two, six, 24 and 48 hours postoperatively. There was no significant difference in adverse events between groups; only three trials reported less sedation in the NSAID group. Many potential adverse effects were not reported by the trials.

In the subgroup analyses, non-selective NSAIDs produced better pain relief than selective COX-2 NSAIDs (WMD -14.4, 95% CI -19.0 to -9.9 versus -3.7, 95% CI -6.8 to -0.6). Pain relief was better in patients who underwent discectomy compared to patients who underwent spinal fusion (WMD -18.1, 95% CI -25.2 to -10.9 versus -7.0, 95% CI -9.8 to -4.2) and in patients on non-PCA morphine drugs compared to those on PCA morphine (WMD -19.0, 95% CI -26.9 to -11.1 versus -7.1, 95% CI -9.7 to -4.5). There was no significant difference based on trial quality. With respect to cumulative opioid consumption, there was no significant difference between patients on non-selective or selective COX-2 NSAIDs. Opioid consumption was reduced significantly more in the spinal fusion group than with the other types of surgery (WMD -30.7, 95% CI -42.2 to -19.1 versus -6.7, 95% CI -16.1 to -2.7). There was no significant difference in opioid consumption between groups based on type of opioid or quality of studies. Sensitivity analyses did not significantly affect the direction or magnitude of the results.

**Authors’ conclusions**

The meta-analysis provided evidence that NSAIDs plus opioids provided superior analgesia in terms of pain scores and opioid consumption than opioids alone in patients who underwent lumbar spine surgery (discectomy, laminectomy or spinal fusion). There was no decrease in adverse effects in the NSAID groups.

**CRD commentary**

This was a rigorously conducted and well-reported systematic review that addressed a clearly stated research question. Appropriate inclusion criteria were defined and measures were taken to avoid the introduction of error and bias during the review process. A wide range of appropriate databases was searched (grey literature included). There were no language restrictions. Where required, authors were contacted for missing data. Methods of study selection were not reported. Methodological quality of the included studies was assessed and the results were incorporated in the meta-analysis. Classification of studies according to quality was quite limited, with any studies that did not receive the lowest number of points being rated as high quality. Studies were described in sufficient detail and appropriate subgroup and sensitivity analyses were carried out, but these were interpreted cautiously. Most studies were reported to be good quality, but studies were also small and none had more than 45 patients in any one comparison group. There was a high degree of heterogeneity between the studies.

The authors’ conclusions that pain relief was enhanced with addition of NSAIDs to opioid analgesia appear to be supported by the data presented (most of the studies showed this effect, despite heterogeneity). The authors stated that many relevant adverse events were not reported, so the conclusion for adverse events was less certain, although data
seemed to suggest that there was no reduction in adverse events with NSAIDs.

The review included several trials which were subsequently retracted.

**Implications of the review for practice and research**
The authors made no specific recommendations for practice.

**Research**
The authors stated that further well-designed large trials were required to confirm the findings of the review.

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