Analgesic treatment after laparoscopic cholecystectomy: a critical assessment of the evidence

Bisgaard T

CRD summary
The review assessed treatments for pain relief after laparoscopic cholecystectomy. The author concluded that treatment should consist of a dose of dexamethasone before surgery together with local anaesthetics at the incision and non-steroidal anti-inflammatory drugs or cyclooxygenase-2 inhibitors for a few days after surgery. The conclusions went beyond the evidence, which was systematically reviewed and might not be impartial.

Authors’ objectives
To propose a multimodal strategy for analgesia for acute pain following laparoscopic cholecystectomy.

Searching
MEDLINE, EMBASE and the Cochrane Library were searched from 1985 to 2005 for studies published in English language journals; the search terms were reported. Additional studies were identified by checking the references in reviews and original articles.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies of analgesia were eligible for inclusion. The included interventions were non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, incisional and intraperitoneal local anaesthetics, opioids, steroids, epidural analgesics, gabapentin, clonidine, N-methyl-D-aspartate (NMDA) receptor antagonists and multimodal strategies. The instillation site, timing, volume and dose (25 to 380 mg) of local anaesthetics varied between the included studies. Most of the included studies were placebo-controlled, while some compared alternative regimens. The specific drugs used in some studies were reported.

Participants included in the review
Studies in patients undergoing laparoscopic cholecystectomy were eligible for inclusion. No further details about the participants in the included studies were reported.

Outcomes assessed in the review
The main outcome of interest appeared to be post-operative pain. The author restricted the conclusions to findings from principal analgesic outcome trials, a criterion that was not clearly defined in the review but appeared to refer to trials in which the primary outcome was post-operative pain. The outcomes reported were postoperative pain measured on a visual analogue or verbal rating scale, opioid needs, and pain categorised as incisional, visceral or shoulder pain. Adverse effects outcomes were reported only for the two trials that the author conducted.

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

Assessment of study quality
The quality of the included studies was assessed using a validated form and the following criteria: whether the trial had a stated aim, adequate control group and statistics, description of the selection process, method of randomisation, baseline equivalence, description of the intervention and operation, defined end point, unbiased assessment and adequate post-operative follow-up. A composite score was used to categorise trials as poor, moderate or ideal (good) quality. The included studies were apparently evaluated by the author, except for the two trials he conducted which
were evaluated by an independent assessor.

Data extraction
The author did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

The data were expressed as either a significant difference or no significant difference between the treatment and control.

Methods of synthesis
How were the studies combined?
The included studies were grouped according to the type of intervention and listed in tables, using symbols to denote significant and no significant difference in outcomes between treatment and control, together with a narrative critique of the findings. In addition, the effects of treatment on incisional, visceral and shoulder pain were summarised across the included studies. The conclusions were said to be based on studies of good or moderate quality.

How were differences between studies investigated?
Studies of local anaesthetics were grouped as incisional, intraperitoneal or both versus placebo, or incisional versus intraperitoneal. The remaining studies were grouped under NSAIDs/COX-2 inhibitors, opioids, steroids, epidural analgesia, intrathecal local anaesthetic/morphine, gabapentin, clonidine, NMDA receptor antagonists, or multimodal analgesia.

Results of the review
Sixty-four RCTs (5,018 participants) were included in the review.

NSAIDs/COX-2 inhibitors.
Six trials of NSAIDs and two of COX-2 inhibitors showed significant effects on pain and/or opioid needs compared with placebo. Study quality was moderate or poor in all but one trial. One poor-quality trial showed no difference between NSAIDs and acetaminophen (paracetamol). Pre-operative intravenous ketoprofen significantly reduced pain and opioid needs in comparison with post-operative administration (1 good-quality trial).

Local anaesthetics.
Six out of 8 trials of incisional local anaesthetics showed a significant effect on pain compared with placebo, while treatment had a significant opioid-sparing effect in 4 trials. The quality of these trials was moderate or poor.

The effect of intraperitoneal local anaesthetics on pain and opioid needs was inconsistent across 24 trials. Fifteen trials (1 good quality) showed a significant difference in at least one outcome in favour of treatment compared with placebo, whereas 9 trials (1 good quality) found no difference. The trial protocols varied considerably.

Two good-quality trials of incisional and intraperitoneal local anaesthesia together showed a significant effect on incisional pain, but not on shoulder or visceral pain. In one of the trials overall pain and opioid need was reduced in the first 2 or 3 hours after surgery. The trials varied in the dose, site and timing of the intervention.

Opioids.
Opioids were compared with placebo in 3 trials. One poor-quality trial showed a significant reduction in the need for additional opioids but no effect on pain, whereas 2 moderate-quality trials found no difference in either outcome. Opioids were compared with alternative opioid regimens in 4 trials. One good-quality trial showed better post-operative pain control when treatment was given at the beginning rather than at the end of surgery. One good-quality trial showed a significant effect on both outcomes with intraperitoneal versus intramuscular pethidine. Two moderate-quality trials found no difference in effect between alternative regimens.
Steroids.

One good-quality placebo-controlled trial of dexamethasone showed a significant reduction in overall, incisional and visceral pain, but not shoulder pain, and a significant reduction in opioid needs.

Epidural analgesics.

Pain was significantly reduced by epidural analgesia compared with unspecified controls in 2 poor-quality trials. Pain and opioid needs were significantly reduced by intrathecal local anaesthesia/morphine in one moderate-quality placebo-controlled trial.

Gabapentin.

Pre-operative gabapentin significantly reduced pain and opioid consumption compared with placebo or tramadol in one moderate-quality trial.

Clonidine.

Clonidine was compared with placebo in 2 poor-quality trials. One showed that treatment significantly reduced post-operative pain. Both trials showed a significant difference in opioid needs.

NMDA receptor antagonists.

Significant beneficial effects on pain and opioid needs were shown in 3 trials of dextromethorphan compared with placebo and/or intravenous lidocaine or tramadol. The trials were of moderate or poor quality. Two trials, one poor and one moderate quality, found no difference between ketamine and placebo or tramadol.

Multimodal strategies.

Multimodal analgesia comprising pre-operative intramuscular opioids, ketorolac, and incisional-intraperitoneal local anaesthetic blockade significantly reduced pain and opioid needs compared with placebo in one moderate-quality trial.

Interventions to reduce incisional, visceral and shoulder pain.

Few trials investigated the different components of post-operative pain following laparoscopic cholecystectomy. On the basis of the aforementioned studies included in the review, incisional local anaesthetics and dexamethasone reduced incisional pain, while intraperitoneal local anaesthetics and dexamethasone reduced visceral pain. Evidence for the treatment of shoulder pain was lacking.

Authors' conclusions

Analgesic treatment after laparoscopic cholecystectomy should be multimodal and consist of a pre-operative single dose of dexamethasone, incisional local anaesthetics at the start or at the end of surgery, and regular NSAIDs or COX-2 inhibitors in the first 3 to 4 days following surgery.

CRD commentary

The review question was defined in broad terms. As it appeared to have been conducted by a single author and lacked information on how the studies were selected it raised concern about the potential for selection bias. Although the search was adequate, the restriction to English language publications might have introduced publication as well as language bias. A thorough assessment of the quality of the included studies appeared to have been carried out, largely by a single person, and the use of composite scores lacked transparency. Insufficient details about the included studies were reported. The analysis focused on statistical significance without presenting the actual data. Evidence from sources other than the studies included in the review was incorporated in the overall results and conclusions.

The evidence reviewed did not directly support a specific multimodal strategy, although the individual elements within
the author's conclusion appeared to be generally consistent with the findings from the included studies. Caution is also warranted in the interpretation of the conclusion, given the limitations in the review methods and reporting and the scarcity of good-quality studies.

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

**Practice:** The author stated that analgesic treatment should be multimodal and consist of a pre-operative single dose of dexamethasone, incisional local anaesthetics at the start or at the end of surgery, and regular NSAIDs or COX-2 inhibitors in the first 3 to 4 days following surgery. Opioids are not recommended unless other analgesic techniques fail. It should be noted that the evidence reviewed did not directly support a multimodal approach and the review author recommended further research on the multimodal approach.

**Research:** The author stated that multimodal analgesic therapy should be tested against placebo and that more dose-response information is need with respect to incisional local anaesthetics, NSAIDs and COX-2 inhibitors. The clinical implications of pain relief and opioid-sparing effects should be investigated further. RCTs to evaluate aspects of steroid therapy were suggested, as were future studies concerning chronic pain.

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