

# Systematic review of the efficacy and safety of peri-operative analgesic techniques in laparoscopic cholecystectomy

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## Background and Goal of Study

- Clinical practice in the management of postoperative pain frequently differs between centres, and local policies may not always reflect best evidence-based practice.
- Although two systematic reviews have examined the role of intraperitoneal, port-site and incisional analgesia in laparoscopic procedures,<sup>1,2</sup> and a further two systematic, qualitative reviews have examined laparoscopic cholecystectomy studies in which analgesia was an endpoint,<sup>3,4</sup> a systematic review of laparoscopic cholecystectomy studies including meta-analysis as well as qualitative analyses has not been performed.
- The objective of this systematic review was to compare the efficacy and safety of analgesic, anaesthetic and operative techniques aimed at influencing postoperative pain in adult patients undergoing laparoscopic cholecystectomy.

## Materials and Methods

- The review was conducted according to the methods of the Cochrane Collaboration.<sup>5</sup>
- MEDLINE was searched from 1966–June 2002 and Embase from 1988–June 2002 using predefined search criteria and reference lists of identified studies were also searched for further references. Articles were only considered for inclusion where they were in the English language.
- Studies eligible for inclusion were:
  - Those in which all patients or a definable subgroup underwent laparoscopic cholecystectomy.
  - Randomised trials of operative analgesia compared with either placebo or other methods of operative analgesia and anaesthesia aimed at influencing postoperative pain, and randomised trials of operative techniques conducted to examine their effect on postoperative pain.
  - Double-blinding was required for all types of operative analgesia except neuraxial routes of administration where the placement of a catheter for placebo administration would be considered unethical.
  - The use of visual analogue scale (VAS) or verbal rating scale (VRS) was required for inclusion.
- Meta-analysis was conducted on mean differences in postoperative VAS scores grouped for 0–6 hours, 6–12 hours and 12–24 hours. VRS scores were converted to VAS scores.
- The issue of the value of pre-emptive analgesia was examined by grouping studies that contained arms with pre- and postoperative administration of the same agent or technique.

## Results

- Fifty-nine studies were included for analysis and 70 studies were excluded. The most common reason for exclusion was the use of open, rather than laparoscopic, cholecystectomy.
- The following studies and outcomes of peri-operative analgesic techniques were identified:
  - Intraperitoneal (ip) local anaesthetic (LA) vs. no such therapy (16 studies, n=521 active, 411 control).<sup>6,21</sup> Nine studies demonstrated a significant advantage for ip therapy in reducing VAS scores, whilst 7 did not. Meta-analysis demonstrated a highly significant benefit for ip analgesia vs. control in the 0–6 hour group (weighted mean difference (WMD) -1.44 [95% C.I. -1.69, -1.18], p<0.00001, Figure 1) with a non-significant benefit in the 6–12 and 12–24 hour groups (WMD -0.76 [-1.64, 0.11], p=0.09 and -0.52 [-1.55, 0.52], p=0.3, respectively). Five studies reported a significant advantage for ip analgesia vs. control on the use of supplementary analgesia, and 9 did not. Meta-analysis showed that ip analgesia was not

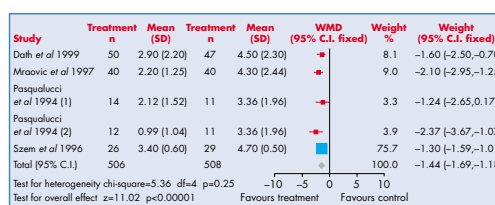


Figure 1. VAS scores for intraperitoneal (ip) local anaesthetic (LA) vs. no such therapy\* (WMD = weighted mean difference)

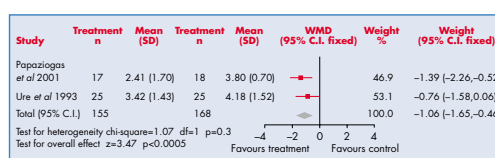


Figure 2. VAS scores for incisional local anaesthetic vs. no such therapy (0–6 hours)\* (WMD = weighted mean difference)

associated with a significant benefit in reducing morphine consumption (WMD -12.27 [-29.20, 4.65], p=0.16). Although ip analgesia had no significant benefit in reducing the incidence of nausea or vomiting in five studies (remainder not reported), meta-analysis showed that it was associated with a significant benefit in reducing nausea (odds ratio 0.53 [0.35, 0.81], p=0.003) but not vomiting (odds ratio 0.54 [0.28, 1.05], p=0.07).

- Incisional local anaesthetic (LA) vs. no such therapy (6 studies, n=185 active, 133 control).<sup>10,22,26</sup> Five studies (including one that utilised a small intraperitoneal injection of LA) demonstrated a significant benefit for incisional analgesia on reducing VAS scores whilst the sixth showed no benefit. Meta-analysis showed a significant benefit for incisional analgesia in the 0–6 hour group (WMD -1.06 [-1.65, -0.46], p<0.0005, Figure 2), the 6–12 hour group, (1 study, WMD -1.10 [-1.52, -0.68], p<0.00001) and the 12–24 hour group (WMD -1.47 [-1.92, -1.02], p<0.00001, Figure 3). Incisional analgesia also reduced the use of supplementary analgesics in four studies, with two showing no significant benefit. Although only one study reported a significant benefit for incisional analgesia on reducing the incidence of postoperative nausea, meta-analysis showed a significant benefit (odds ratio 0.33 [0.17, 0.65], p=0.001).
- Epidural local anaesthetics (LA) vs. no such therapy (2 studies, n=37 active, n=39 control).<sup>27,28</sup> Both studies demonstrated a significant benefit for epidural analgesia vs. control in reducing VAS scores and the use of supplementary analgesia.
- NSAIDs vs. no such therapy (7 studies, n=312 active, n=160 control).<sup>29,34</sup> Six of the 7 studies reported superiority for NSAIDs vs. control in reducing VAS scores. For the meta-analysis, consistent data were available for 0–4 hours

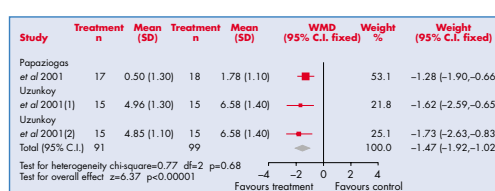


Figure 3. VAS scores for incisional local anaesthetic vs. no such therapy (12–24 hours)\* (WMD = weighted mean difference)

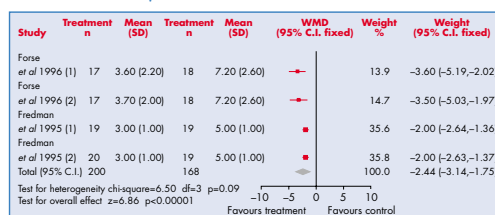


Figure 4. VAS scores for NSAIDs vs. no such therapy (0–4 hours post-op)\* (WMD = weighted mean difference)

postoperatively. A significant benefit for NSAID therapy was observed compared with control (WMD -2.44 [-3.14, -1.75], p<0.00001, Figure 4). Four studies reported time to first analgesic request, all showing a significant advantage for the NSAID groups vs. control and 6 studies reported the use of supplementary analgesics all showing a significant advantage for the NSAID groups. NSAIDs were associated with a significantly lower incidence of postoperative vomiting compared with control (odds ratio 0.45 [0.21, 0.95], p=0.04), but not nausea (odds ratio 0.68 [0.36, 1.27], p=0.2).

- Combined epidural/general anaesthesia (CEGA) vs. total intravenous anaesthesia (TIVA) (1 study, n=20 active, n=20 control).<sup>35</sup> CEGA was superior to TIVA for reducing VAS scores in this single study.
- Pre-emptive vs. postoperative administration. Of the six studies included in this analysis, two reported a significant benefit for pre-emptive analgesia vs. postoperative analgesia in reducing VAS scores, whilst the remaining four found no significant difference. A limited meta-analysis found no significant benefit for pre-emptive analgesia vs. postoperative analgesia (WMD -0.94 [-3.01, 1.12], p=0.4).

## Conclusions

- Intraperitoneal and incisional LA, and NSAIDs, reduced pain scores significantly compared with controls.
- Incisional LA acts longer acting than intraperitoneal LA.
- Meta-analysis demonstrated the benefit of epidural analgesia, although the clinical utility of this procedure in laparoscopic cholecystectomy is doubtful.
- Pre-operative analgesia did not offer a significant advantage over postoperative administration.
- There was no clear evidence of the role of anaesthetic regimens in reducing postoperative pain.
- A number of commonly used modes of analgesia (e.g. paracetamol) have not been examined in randomised studies in laparoscopic cholecystectomy.
- Further data are needed on the combination of techniques, and the potential role of patient baseline and surgical factors, in predicting postoperative pain outcomes.

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