A systematic review of interventions to facilitate ambulatory laparoscopic cholecystectomy

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Abstract

Objectives: We aimed to perform a systematic review of the literature to identify interventions that may facilitate ambulatory laparoscopic cholecystectomy (LC).

Methods: The PubMed and CENTRAL databases were interrogated for key MeSH headings. To be eligible for systematic review, trials were required to include outcome measures of postoperative pain, nausea or vomiting and time to discharge following LC. Interventions were subsequently assessed for the level of evidence and grade of recommendation given.

Results: A total of 331 trials were identified, 68 of which met the predefined study inclusion criteria. Interventions which met Level I, Grade A recommendation included the administration of 8 mg i.v. dexamethasone, preoperative administration of analgesia including the use of non-steroidal anti-inflammatory or COX II inhibitors, intraoperative use of an anti-emetic, pre-incisional use of bupivacaine, administration of intraperitoneal bupivacaine on establishment of pneumoperitoneum, and avoidance of drains.

Conclusions: High-quality evidence describing interventions that minimize barriers to ambulatory LC exists. Further studies will be required to determine the optimal combination of these interventions.

Keywords
day-case cholecystectomy, dexamethasone, intraperitoneal local anaesthetic, postoperative nausea and vomiting

Received 6 June 2011; accepted 9 July 2011

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Introduction

Laparoscopic cholecystectomy (LC) is currently accepted as the reference standard for the management of symptomatic or complicated gallstone disease. There is now increasing evidence to support ambulatory LC as the standard of care as a result of its ability to improve patient recovery and significantly reduce hospital stay.¹–⁴ Laparoscopic cholecystectomy would appear to be an ideal operation for ambulatory surgery because it is of short duration, uses small incisions, carries a low rate of immediate complications and does not disrupt gastrointestinal homeostasis. Despite this, several series describing ambulatory LC have reported inpatient admission rates of up to 20%, mainly for nausea, vomiting or uncontrolled pain.⁵–⁷

The aim of this study was to develop an evidence-based approach to ambulatory LC by systematically reviewing all published randomized controlled trials (RCTs) of pre-, intra- and postoperative interventions aimed at improving postoperative pain, postoperative nausea and vomiting (PONV), patient satisfaction and general well-being following LC.

Materials and methods

Search strategy
The search sought to identify published RCTs analysing the efficacy of preoperative (initiated prior to anaesthetic room), intraoperative (initiated in the anaesthetic or operating room) and
postoperative (initiated in recovery or beyond) interventions during LC that can optimize early discharge and enhance patient recovery.

A search of the PubMed and CENTRAL (Cochrane Central Register of Controlled Trials) databases for materials published from 1990 to December 2009 was performed using the following key MeSH terms: cholecystectomy; laparoscopic; laparoscopic cholecystectomy.mp; ambulatory surgical procedures/; anaesthesia/; preoperative care/; postoperative care/; intraoperative care/; patient education as topic/ OR patient education.mp, and drainage/ OR drainage.mp. The search was limited to studies published in the English language, studies in humans and RCTs.

Eligibility criteria
This search was based on two hypotheses: firstly, that ambulatory LC would prove to be feasible, safe and effective, and, secondly, that pain, PONV and other postoperative complications resulting in low levels of patient satisfaction would emerge as barriers to ambulatory LC. Publications debating the above hypotheses were excluded. Other exclusion criteria were: (i) a focus on comparisons of patient characteristics as predictors of success in ambulatory LC; (ii) indistinguishable or mixed-participant populations of LC patients with other surgical patients; (iii) primary outcome measures other than postoperative pain, PONV, patient satisfaction, time to discharge or other determinants of discharge of patients postoperatively; (iv) publication in languages other than English; (v) non-human participants; (vi) non-RCT formats, and (vii) studies with a Jadad score of <3.

Study selection
Initial selection
Potential articles were identified by the search strategy described above. Their titles and abstracts were manually screened by the primary reviewer and the eligibility criteria were applied. Any contentious issues were then resolved by the consensus of all authors. Duplicate studies and studies that did not meet eligibility criteria were then excluded.

Data extraction
Eligible manuscripts were analysed according to data extraction completed as described in the Appendix and allocated a Jadad score. Publications with a Jadad score of <3 were subsequently excluded from review. Consensus on Jadad scores was achieved by at least two authors.

A summary statement for each intervention was constructed on the calculated strength of evidence (Table 1) and grade of recommendation (Table 2).

Results
The search yielded 331 potential articles; 263 articles were excluded from the analysis as they did not meet the inclusion criteria (Fig. 1). Of the 68 manuscripts included for analysis, 28 (41%) had a Jadad score of 3, 23 (34%) had a score of 4, and 17 (25%) had a score of 5.

Preoperative interventions
Correction of preoperative dehydration is likely to be beneficial (Level IB)
Two well-conducted studies assessed the effect of preoperative carbohydrate (CHO) drinks with divergent conclusions. Importantly, the two trials differed in their anaesthesia protocols. In the trial in which significant improvements in postoperative parameters were measured, patients received an increased volume of intraoperative i.v. fluid compared with patients in the trial in which no significant difference was observed. Hence the routine use of preoperative CHO drinks cannot currently be recommended and further studies are indicated. In an effort to assess the effect of preoperative dehydration, Adanir et al. performed a double-blind RCT (n = 210) comparing pre- and intraoperative i.v. fluid replacement for an assumed fluid deficit caused by an overnight fast. This well-powered study showed that PONV was significantly reduced in those receiving preoperative rehydration (48%) compared with those receiving intraoperative replacement alone (64%).

Dexamethasone 8 mg i.v. should be given preoperatively (Level IA)
Seven randomized trials assessed the effect of dexamethasone on PONV. All seven trials used 8 mg of i.v. dexamethasone as the
standard dose, although the timing of dexamethasone administration varied from as early as 90 min preoperatively to as late as induction of anaesthesia. The incidence of PONV ranged from 58% to 75% in the placebo groups and from 20% to 35% in the dexamethasone groups. In two trials,20,21 dexamethasone was given in addition to a serotonin receptor antagonist, resulting in a 3–5% incidence of PONV, compared with a 17–18% incidence in the group receiving a serotonin antagonist alone. Interestingly, two of the placebo-controlled trials20,23 showed a significant reduction in postoperative pain scores with the administration of an anti-emetic. In both trials, dexamethasone was administered 90 min prior to surgery, whereas in the two placebo-controlled trials,17,22 in which no reduction in postoperative pain scores was observed with dexamethasone, it was administered at anaesthetic induction. Favourable outcomes appear to be limited to dexamethasone as an equipotent dose of oral prednisone (50 mg) showed no significant difference in outcomes measured.24

Patient education improves knowledge and recall but does not affect postoperative pain or PONV (Level IIB)
Two randomized trials25,26 analysed the effect of preoperative patient education. Although both trials showed that education increased patient knowledge recall, neither showed an improvement in postoperative pain scores or PONV.

Preoperative administration of NSAIDs or COX II inhibitors is indicated (Level IA).
A multimodal approach may have an additive effect (Level IB)
In total, nine studies addressed the role of single-agent preoperative analgesia in improving postoperative outcomes. Three

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Figure 1 Results of search strategy and application of exclusion criteria for randomized trials assessing interventions that will facilitate ambulatory laparoscopic cholecystectomy. RCT, randomized controlled trial.
studies\textsuperscript{27–29} compared non-steroidal anti-inflammatory drugs (NSAIDs) with placebo. All three studies showed decreased postoperative pain scores and a reduced requirement for postoperative opioid analgesia. Four trials\textsuperscript{28–32} evaluated COX II inhibitors. All four trials showed a reduction in postoperative pain and two trials\textsuperscript{30,31} reported increased patient satisfaction.

Yu et al.\textsuperscript{33} administered clonidine 150 mcg orally 60–90 min prior to anaesthetic induction and showed that patients in the clonidine group required less analgesia in the first 24 h postoperatively compared with those in the placebo group. Similarly, the analgesic efficacy of a γ-aminobutyric acid analogue, pregabalin, significantly reduced postoperative pain in a single trial.\textsuperscript{34}

Five trials\textsuperscript{35–39} described outcomes in patients receiving multimodal analgesia. They used a variety of analgesic combinations which included NSAIDs, COX II inhibitors, oxycodone, gabapentin, local anaesthetic and intrathecal morphine and thus are not directly comparable. However, four of these trials\textsuperscript{39–39} showed a significant reduction in postoperative pain without a reduction in PONV. In a trial reported by Gilron et al.\textsuperscript{39} no reduction in postoperative pain scores was seen in patients receiving a multimodal approach compared with those receiving a single agent alone.

**Intraoperative interventions**

A liberal intraoperative fluid regimen is superior to a restrictive approach (Level IB)

Holte et al.\textsuperscript{40} conducted a double-blind RCT of 48 patients undergoing elective LC. The aim of the study was to compare two different intraoperative i.v. fluid regimens of, respectively, a liberal (40 ml/kg) and a restrictive (15 ml/kg) administration of lactated Ringer’s solution. The results overwhelmingly favoured the liberal intraoperative fluid regimen, in which all physiological subjective recovery measures and clinical outcomes were significantly improved. Although the study was underpowered, hospital stay in the liberal i.v. fluid group was significantly shorter than that in the restricted-fluid group [i.e. of the patients eligible for same-day discharge, 21 of 22 patients in the liberal i.v. fluid group were discharged compared with only 15 of 23 in the restricted-fluid group (P = 0.02)]. It should be noted that this trial applied significant exclusion criteria which excluded half the patients in the liberal i.v. fluid arm from analysis for reasons of significant cardiovascular comorbidity.

Intraoperative magnesium or esmolol infusion may be useful in reducing postoperative pain (Level IB)

One trial examined the effect of an intraoperative magnesium infusion on postoperative pain following LC. Mentes et al.\textsuperscript{41} randomized 83 patients to receive either a 50-mg/kg infusion of magnesium sulphate (MgSO\textsubscript{4}) or placebo. The treatment group showed significant reductions in postoperative pain scores and significantly reduced patient-controlled analgesia use. A further trial assessed the effect of an esmolol infusion and found that it reduced PONV, decreased postoperative pain and led to earlier discharge.\textsuperscript{42}

Pneumoperitoneal pressure of \(\leq 9\) mmHg may be useful in reducing postoperative pain scores (Level IB)

Five trials\textsuperscript{43–46} assessed the effect of pneumoperitoneum on postoperative pain. Low-pressure pneumoperitoneum was defined as pressure of 7–9 mmHg and standard pressure as pressure of 12–13 mmHg. Although three trials\textsuperscript{44–46} showed reduced pain scores with low-pressure pneumoperitoneum, two trials did not. These included a well-powered study\textsuperscript{44} and a further trial performed in patients undergoing ambulatory cholecystectomy.\textsuperscript{45}

Pre-incisional local anaesthesia to wounds and peritoneum should be used (Level IA)

Thirteen trials\textsuperscript{48–60} examined the use of local anaesthesia (LA) during LC. Intra-peritoneal LA was shown to be beneficial in seven of nine trials.\textsuperscript{48–50} In two trials,\textsuperscript{51,52} in which no difference emerged, LA was administered at the end of the procedure. Karasalan et al.\textsuperscript{52} showed the effect of LA to be greatest when it was administered at the commencement of pneumoperitoneum. Alkhamesi et al.\textsuperscript{53} showed aerosolized LA to be more effective than injected intra-peritoneal LA. Eight trials\textsuperscript{51,53,55–60} examined the effect of incisional LA, including two\textsuperscript{53,57} which combined this with intra-peritoneal LA. Of these trials, only two did not show a significant benefit with incisional LA and one\textsuperscript{53} of these administered it postoperatively. Pre-incisional LA has been shown to be superior to post-incisional infiltration.\textsuperscript{55} Although Ure et al.\textsuperscript{56} concluded no effect from pre-incisional LA, they reported a significant increase in the number of pain-free patients in the postoperative period. Two trials\textsuperscript{53,57} showed that the combination of intra-peritoneal and incisional LA is superior to either method alone and reduces PONV.\textsuperscript{57}

Intra-abdominal drains should not be used routinely (Level IA)

Three trials examined the effect of placing an intra-abdominal drain. Two of these trials\textsuperscript{54,55} placed sub-hepatic drains. Both were well powered and showed a significant increase in postoperative pain using a visual analogue scale (VAS) in patients in whom sub-hepatic drains were placed compared with controls. In the third trial, Nursal et al.\textsuperscript{56} placed sub-diaphragmatic drains with the aim of removing residual gas following pneumoperitoneum. No differences in use of postoperative analgesia or anti-emetics were observed.

Other intraoperative interventions

Other intraoperative interventions aimed at reducing postoperative pain included two trials\textsuperscript{65,66} assessing the effect of ketamine. Neither trial showed any clinically significant improvement in postoperative pain. Boccarda et al.\textsuperscript{65} found that ketoprofen given just prior to induction was superior to both ketoprofen given at the end of the procedure or propacetamol, further supporting the use of preoperative NSAIDs. Cekmen et al.\textsuperscript{66} studied the efficacy of transcutaneous electrical nerve stimulation (TENS) on PONV.
and found it to be effective in reducing PONV and decreasing the need for analgesia and anti-emetics (Level IIB).

Anti-emetics significantly reduce PONV (Level IA). Serotonin antagonists droperidol, metoclopramide, gabapentin and dixyrazine are all effective in reducing PONV (Level IB). Total i.v. anaesthesia combined with anti-emetics significantly reduces PONV compared with either alone (Level IB).

Two trials compared volatile anaesthesia with total i.v. anaesthesia (TIVA). Both showed that patients receiving TIVA took longer to achieve eye opening in recovery; however, this did not translate to a significant delay in discharge from either recovery or hospital. Additionally, Raeder et al. showed a significant reduction in PONV and pain in those who received TIVA, a finding further supported by Habib et al. In this study, patients receiving a multimodal approach to PONV with anti-emetics and propofol were shown to have a significantly lower incidence of PONV and increased satisfaction with the management of their PONV compared with those receiving propofol alone or inhalational anaesthesia with anti-emetics.

Eight studies evaluated the efficacy of different anti-emetic regimens in patients undergoing LC. Two placebo-controlled trials showed serotonergic antagonists such as ondansetron to be effective in reducing postoperative nausea and vomiting. Additionally, three studies compared ondansetron with droperidol, metoclopramide or both and found no differences. In a randomized, placebo-controlled trial of 250 patients undergoing LC, Pandey et al. assessed the efficacy of 600 mg gabapentin on PONV in the first 24 h. They found a statistically significant reduction in the incidence of PONV in the gabapentin group, but the severity of PONV was similar in both groups. Additionally, in patients given gabapentin, fentanyl requirements were reduced, which is consistent with the previously reported opioid-sparing effects of this treatment.

The efficacy of dixyrazine, a phenothiazine derivative, was studied by Glaser et al. in a trial of 197 patients. The authors reported significantly more patients without PONV and fewer patients requiring rescue analgesia in the dixyrazine group.

Other anaesthetic techniques trialled have included epidural and regional anaesthesia. Only intercostal nerve blocks have been shown to reduce postoperative pain scores, although their clinical significance was debatable (Level IB).

**Postoperative interventions**

One RCT examined the effect of postoperative melatonin. Although the treatment group showed a reduction in sleep latency, no improvement in sleep quality, fatigue or generalized well-being emerged and therefore the authors concluded that this treatment could not be recommended (Level IB).

In an RCT of 73 patients, Puolakka et al. assessed the efficacy of parecoxib 40 mg vs. 80 mg placebo. All study drugs were administered at the end of anaesthesia. No significant differences between the groups emerged with respect to postoperative fentanyl consumption, incidence of PONV or use of anti-emetics. Despite the results of this well-powered study, it analysed outcomes at 20 h postoperatively and the authors acknowledged that this may not have been a long enough timeframe to study the analgesic efficacy of coxibs (Level IIB).

**Discussion**

Laparoscopic cholecystectomy remains one of the most commonly performed general surgical operations in both the acute and elective settings. Despite over two decades of experience, and the procedure's suitability to an ambulatory approach, it has not become widely accepted. Initial attempts at ambulatory cholecystectomy reported high rates of readmission, which may well have impaired its uptake, yet patients report high levels of satisfaction when the procedure is performed well. As enhanced-recovery surgery becomes mainstream for major procedures, it has become clear that the most effective programmes are those which take a multimodal approach to treatment. A total of 68 randomized trials met our study inclusion criteria and five interventions were identified as having evidence strong enough to support a Level IA recommendation.

Despite the large numbers of LC performed on a daily basis around the world, only 22 of the trials examined in this review enrolled over 100 patients. These were powered sufficiently for primary outcome measures, but placed secondary outcome measures at significant risk of type II errors; consequently, further trials are needed.

Pain following LC has been classified into three major types by Joris et al. These include shoulder-tip pain, visceral pain (deep, dull pain that is hard to localize) and parietal pain (surface or wound-type pain). Joris et al. demonstrated that visceral pain features in the first 24 h postoperatively, but is short-lived, whereas shoulder-tip pain is minor and features on postoperative day 2. These findings, however, contrast with those of Sarli et al., who reported that shoulder-tip pain started at 3–6 h postoperatively, peaked at 12 h and rapidly improved thereafter. What is clear is that a single agent is unlikely to treat all three types of pain and a multimodal approach will be required.

Although almost all of the trials that assessed postoperative pain used VAS scores and/or postoperative analgesic requirements, the significant variations in technique, trial design, time at which data were measured and type of postoperative analgesia make it impossible to perform a meta-analysis and make inter-trial comparisons difficult. Similar issues exist in terms of varia-
tions in definitions of PONV, timing of measurement and use of postoperative rescue anti-emetics.

The other significant issue is that many trials showed statistically significant reductions in VAS pain scores which may not truly represent clinically significant reductions in pain. It is generally accepted that a clinically significant result for trials assessing pain should report a 2-point decrease (on a 10-point scale) or a 30% reduction in VAS scores. Similarly, when pain is considered to be ‘mild’ to begin with (i.e. as reflected by a pain score of <4/10), it may be difficult to interpret any reduction as clinically meaningful. Future trials may need to overcome this by using more clinically relevant outcome measures, such as time to discharge or time to return to normal activities, as primary endpoints.

A further significant trend concerned the impact of the timing of the intervention on postoperative pain. It would seem that pre-emptive administration is important if the intervention is to be effective. For example, seven trials attempted to determine the effect of dexamethasone on PONV: in two trials, in which the treatment was administered 90 min prior to induction, significant reductions in postoperative pain scores were observed, but these effects were not seen when dexamethasone was given at induction. Similarly, preoperative analgesia, pre-incisional use of local anaesthetic, and administration of intraperitoneal local anaesthetic as soon as pneumoperitoneum is established and prior to performing cholecystectomy all appear to be important if the intervention is to be effective.

From the data assessed, it is clear that multiple interventions have been shown to be effective in improving outcomes following LC. Although multimodal interventional trials have been identified and many of these used a standardized approach, none included all of the interventions identified as useful. Many studies investigating PONV included the use of agents known to be emetogenic such as nitrous oxide, neostigmine and even volatile anaesthesia. If the goal of the intervention is early discharge, it would make sense to use agents that are not associated with PONV.

It is therefore unclear which combination of interventions is necessary to achieve optimal rates of ambulatory LC. Given the high number of potential interventions, it would seem unlikely that an RCT could be designed to establish the optimal combination of interventions. Instead, it may be more practical and timely to design a clinical pathway or protocol which combines these evidence-based interventions and which measures predefined dichotomous outcomes, such as successful discharge within 6 h or 12 h, and time to return to work. Interventions could then be added or subtracted, their effects measured and analysed, and appropriate recommendations made.

Acknowledgement
This systematic review was made possible by funding (NZ$4000) awarded to YA by the New Zealand Medical Association through its Summer Studentship Programme.

Conflicts of interest
None declared.

References


Appendix

Protocol for the systematic review of factors facilitating ambulatory laparoscopic cholecystectomy

Objective
To identify preoperative, intraoperative and postoperative interventions to optimize the success of ambulatory cholecystectomy.

Hypotheses
1. That ambulatory laparoscopic cholecystectomy is feasible, safe and effective
2. That pain, postoperative nausea and vomiting and low levels of patient satisfaction are barriers to ambulatory laparoscopic cholecystectomy

Literature search
Databases searched: OVID PubMed and CENTRAL (Cochrane Central Register of Controlled Trials) using the following strategy:
1. Search term: cholecystectomy, laparoscopic/OR laparoscopic cholecystectomy.mp
2. Search term: ambulatory surgical procedures/
3. Search term: anaesthesia/
4. Search term: preoperative care/
5. Search term: postoperative care/
6. Search term: intraoperative care/
7. Search term: patient education as Topic/ OR patient education.mp
8. Search term: drainage/ OR drainage.mp
9. Limited to English-language studies
10. Limited to human studies
11. Limited to randomized controlled trials only

Additionally, any article that was unavailable in full-text online was explored using the ‘find similar’ function. Ovid MEDLINE was used to retrieve full-text articles if they were not available from PubMed.

Search 1 – 1 AND 2 WITH 9, 10, 11. (In CENTRAL, the use of the English language was manually established by reading abstracts)
Search 2 – 1 AND 3 WITH 9, 10, 11
Search 3 – 1 AND 4 WITH 9, 10, 11
Search 4 – 1 AND 5 WITH 9, 10, 11
Search 5 – 1 AND 6 WITH 9, 10, 11
Search 6 – 1 AND 7 WITH 9, 10, 11
Search 7 – 1 AND 8 WITH 9, 10, 11

Inclusion criteria
A study will be included in the systematic review if it meets the following criteria:
1. The participant population is identified as patients undergoing laparoscopic cholecystectomy
2. The studied intervention is compared with a control
3. The primary outcome measure signifies the studied intervention’s efficacy on enhanced recovery and, hence, faster discharge from hospital after the procedure (e.g. postoperative pain, postoperative nausea and vomiting, patient satisfaction, number of hours until discharge)
4. It is published in English

Exclusion criteria
A study will be excluded from the review if it meets one or more of the following criteria:
1. It aims to prove the safety, feasibility and/or efficacy of ambulatory laparoscopic cholecystectomy compared with an inpatient procedure
2. It has a mixed-participant population from which the measured outcomes in a laparoscopic cholecystectomy patient population cannot be delineated
3. It investigates patient characteristics as predictors of success in ambulatory laparoscopic cholecystectomy
4. It uses outcome measures other than postoperative pain, postoperative nausea and vomiting, patient satisfaction and time until discharge
5. It is not published in English
6. It is not a randomized controlled trial
7. It achieves a Jadad score of <3

Document selection
1. Record the number of articles identified by each search strategy
2. Reviewer to assess title and abstracts identified from all searches and retain full text of articles considered to meet the inclusion/exclusion eligibility criteria
3 Record the number of articles excluded as not relevant based on the exclusion criteria
4 Reviewer to assess more closely the full manuscripts of retained articles and apply all of the inclusion criteria
5 Record the number of articles excluded by this process
6 Record the number of full-text articles retained and evaluated for full analysis

**Data extraction**
The following data will be extracted:
1 Author(s)
2 Year of publication
3 Number of participant population
4 Participant characteristics
5 Randomized controlled trial characteristics
6 Method of randomization
7 Intervention studied
8 Comparison(s) studied
9 Outcome(s) measured
10 Results
11 Conclusions

**Assessment of study quality**
Quality assessment of the studies will be performed using the Jadad Scoring System score. A score of <3 will result in the exclusion of the study from analysis.