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Review Article

PAIN

Evidence-based management of pain after laparoscopic cholecystectomy: a PROSPECT review update

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Abstract

Background: Significant pain can be experienced after laparoscopic cholecystectomy. This systematic review aims to formulate PROSPECT (PROcedure SPECific Postoperative Pain ManagemenT) recommendations to reduce postoperative pain after laparoscopic cholecystectomy.

Methods: Randomised controlled trials published in the English language from January 2006 (date of last PROSPECT review) to December 2017, assessing analgesic, anaesthetic, or operative interventions for laparoscopic cholecystectomy in adults, and reporting pain scores, were retrieved from MEDLINE and Cochrane databases using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) search protocols. PROSPECT methodology was used, and recommendations were formulated after review and discussion by the PROSPECT group (an international group of leading pain specialists and surgeons).

Results: Of 1988 randomised controlled trials identified, 258 met the inclusion criteria and were included in this review. The studies were of mixed methodological quality, and quantitative analysis was not performed because of heterogeneous study design and how outcomes were reported.

Conclusions: We recommend basic analgesic techniques: paracetamol + NSAID or cyclooxygenase-2 specific inhibitor + surgical site local anaesthetic infiltration. Paracetamol and NSAID should be started before or during operation with dexamethasone (GRADE A). Opioid should be reserved for rescue analgesia only (GRADE B). Gabapentanoids, intraperitoneal local anaesthetic, and transversus abdominis plane blocks are not recommended (GRADE D) unless basic analgesia is not possible. Surgically, we recommend low-pressure pneumoperitoneum, postprocedure saline lavage, and aspiration of pneumoperitoneum (GRADE A). Single-port incision techniques are not recommended to reduce pain (GRADE A).

Keywords: analgesia; cholecystectomy; pain, postoperative; multimodal analgesia; opioids

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Editor's key points

- This is a comprehensive PROSPECT review of pain relief after laparoscopic cholecystectomy.
- The authors provide a practical, evidence-based pain relief protocol for laparoscopic cholecystectomy.
- Recommendations highlight the need for multimodal analgesia and reserve opioids for more severe pain.

Laparoscopic cholecystectomy is the mainstay treatment of benign biliary disease. Pain continues to be an important issue after laparoscopic cholecystectomy resulting in prolonged admissions or readmissions.[1] With significant variations in analgesic protocols a unified approach is necessary to provide standardised interventions to reduce pain.

The PROSPECT (PROcedure SPECific Postoperative Pain ManagemenT) Working Group is a collaboration of surgeons and anaesthetists working to formulate specific recommendations for pain management after common but potentially painful operations. The recommendations are based on procedure-specific literature review of systematic reviews and RCTs. The methodology considers clinical practice, efficacy, and adverse effects of analgesic techniques.[2]

This review is an update of a previous PROSPECT review on laparoscopic cholecystectomy published in 2005.[3] Since the last review, there have been a significant number of new randomised controlled trials (RCTs) and reviews on methods to reduce pain after laparoscopic cholecystectomy. This review builds on evidence from the previous review to formulate new recommendations for pain management after laparoscopic cholecystectomy.

Methods

A systematic review was performed for elective laparoscopic cholecystectomy from 2005 to December 2017 using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[4] The literature search methods were identical to the most recent PROSPECT reviews.[5–7] Only minor changes were made to the previously published methods for consistency.[2] Earlier PROSPECT methodology used 'transferable evidence' from similar procedures. Transferable evidence was not used in the current review.

Search strategy

A systematic review of the literature for analgesia after excisional laparoscopic cholecystectomy was conducted of EMBASE, MEDLINE, MEDLINE in process, Cochrane Central Register of Controlled Trials, Cochrane Database of Abstracts or Reviews of Effects, Cochrane Database of Systematic Reviews, and Cochrane NHS Economic Evaluation Database. The search was performed from date of the last review (August 2005) to now (December 2017). Search terms related to pain and interventions for laparoscopic cholecystectomy were: Title and Keyword search for laparoscopic cholecystectom* OR laparoscopy cholecystectomy* AND pain OR pains OR painful* OR painkil* OR pain management OR postoperative pain OR post-operative pain OR analgesi* OR anaesthe* OR anesthe* OR McGill scale OR McGill rating OR McGill pain OR vas OR visual analog* OR vrs OR verbal rating scale* OR nrs OR numerical rating scale* OR pain rating OR epidural OR neuraxial OR intrathecal OR paravertebral OR spinal OR infiltration OR nerve block* OR neural block* OR paravertebral block* OR field block* OR Ilioinguinal block* OR transversus abdominis plane block* OR tap block* OR NSAID* OR nonsteroidal anti-inflammator* OR non-steroidal anti-inflammator* OR COX-2 OR Paracetamol OR acetaminophen OR clonidine OR opioid* OR ketamine OR corticosteroid* OR gabapentin OR pregabalin OR Eutectic Mixture of Local Anesthetics OR EMLA).

In MEDLINE, subject heading search was used for laparoscopic, cholecystectomy, 'Pain, postoperative', 'Pain Measurement', and 'Pain Management'. In MEDLINE search, exploded terms were also used for 'Anesthesia, Conduction', 'Anesthetic, Local', and 'Analgesics'.

The search was limited to RCT, clinical study or trial or review or meta-analysis, English language including only human studies.

Study inclusion and exclusion criteria

Inclusion criteria for studies include RCT and systematic reviews of analgesic, anaesthetic, and operative interventions, published in the English language, addressing pain management relating to laparoscopic cholecystectomy. Moreover, included RCTs should report pain scores using a linear pain scale, for example, visual analogue scale (VAS) or verbal or numerical rating scale (VRS or NRS). We excluded any studies on acute laparoscopic cholecystectomy.

Quality of included studies

All included studies were assessed for quality of reporting of methodology using the PROSPECT Collaboration Methodology:

(i) Numerical scores (total 1–5) for study quality: assigned using the method proposed by Jadad and colleagues,[8] to indicate whether a study reports appropriate randomisation, double-blinding, and statements of possible withdrawals.
(ii) Allocation concealment assessment: indicates whether there was adequate prevention of foreknowledge of treatment assignment by those involved in recruitment (A adequate, B unclear, C inadequate, D not used).
(iii) Statistical analyses and patient follow-up assessment: indicates whether statistical analyses were reported, and whether patient follow-up was greater or less than 80%.
(iv) Additional study quality assessment: including an assessment of how closely the study report meets the requirements of the CONSORT (Consolidated Standards of Reporting of Trials) statement.

Analysis of outcomes and statistical analysis

Summary information for each included study was extracted and recorded in data tables. This information included pain scores, supplementary analgesic use, time to first analgesic request, functional outcomes, and adverse effects. It was assumed that the postoperative pain scores had been assessed at rest, unless otherwise specified in the study report.

The systematic reviews were used to find additional studies via bibliographic screens and aid in formulating recommendations.

The included studies were grouped together based upon the analgesic technique [e.g. epidural analgesia, peripheral nerve blocks, field blocks, surgical site infiltration, paracetamol, non-

steroidal anti-inflammatory drugs, cyclooxygenase-2 (COX-2)-specific inhibitors]. Within each analgesic group, the studies were further placed into subgroups of preoperative, intraoperative, and postoperative interventions. The studies assessing the effects of surgical techniques on analgesic outcomes were grouped separately. The effectiveness of each intervention for each outcome was evaluated qualitatively, by assessing the number of studies showing a significant difference between treatment arms ($P<0.05$ as reported in the study publication).

Quantitative analyses were performed if the studies determined suitable according to the PROSPECT criteria, were homogenous, and data were reported in a suitable manner. In addition, for the studies to be grouped together they should have uniformity in the analgesic technique(s) utilised. Studies that did not report mean and standard deviation data (for continuous variables), or proportion of patients affected (for dichotomous variables), were included in the meta-analyses.

Other sources of information to formulate recommendations

Studies that reported data pooled from patients undergoing mixed surgical procedures and laparoscopic cholecystectomy were excluded from the procedure-specific systematic review.

Information on clinical practice was considered to ensure that the recommendations had clinical validity. The recommendations were formulated by the PROSPECT Working Group, using the Delphi method to collate rounds of individual comments on the evidence and draft recommendations, followed by round-table discussion, and then further Delphi rounds, to achieve final consensus.

Recommendations for optimal pain relief are graded A–D according to the overall level of evidence (LoE), as determined by the quality of studies included, consistency of evidence and source of evidence (Table 1).

Results

PRISMA guidelines were followed for the reporting of this study (Fig. 1). The previous PROSPECT review on laparoscopic cholecystectomy included 121 studies. The recommendations for this review built on the recommendations from the previous review. Using the same search criteria as the previous review, we found an additional 1997 studies, of which 258 RCT and 43 systematic reviews were used to formulate the final recommendations. A total of 200 RCTs were used to justify the recommendations drafted in this review. The included studies examined a multitude of different interventions some with only one supporting RCT. Hence, not all RCTs are referenced and used to formulate final recommendations in this review.

The methodological quality of each study (allocation concealment, Jadad score, and LoE) are summarised in Table 2. For qualitative analysis, the trials were allocated to three broad groups: recommended interventions, not recommended for routine use but may be considered if recommended interventions are not possible, and not recommended for routine administration.

Recommend as the first line for routine use

Paracetamol

Paracetamol has been shown to be effective before, during, and after operation. Two studies have shown significant reduction in pain scores within the first 2 h after operation when an i.v. paracetamol infusion was administered before operation ($P<0.05$).[9,10] However, when i.v. paracetamol was compared with oral administration before operation, there was no significant difference in pain scores in an RCT of 60 subjects (LoE 1).[11] Intraoperative i.v. paracetamol (administered 10 min after induction) reduced pain up to 5 h after operation when compared with placebo ($P=0.01$).[12]

One study that examined pre- and postoperative (for 24 h) i.v. paracetamol infusions compared with dexmedetomidine showed reduced pain for the dexmedetomidine group over the first 24 h after operation ($P<0.05$).[13] However, the paracetamol group still had adequate analgesia with significant less sedation when compared with dexmedetomidine infusions. Paracetamol i.v. showed less pain over the first 24 h when compared with i.v. tramadol alone.[14] Tramadol i.v. was also associated with increased sedation. The tramadol group did not receive routine postoperative paracetamol either i.v. or oral.

Table 1 Grades A–D, based on overall level of evidence (LoE), considering balance of clinical practice information and evidence. NA, not applicable

	Study quality assessments				Grade of recommendation
Study type	Statistical analyses and patient follow-up assessment	Allocation concealment (A–D)	Jadad score	LoE	Procedure specific
Systematic review with homogeneous results	NA	NA	NA	1	A
Randomised controlled trial	Statistics reported and >80% follow-up	A or B	1–5	1	A
Randomised controlled trial	Statistics not reported or questionable, or <80% follow-up	C or D	1–5	2	B
Non-systematic review, cohort study, case study (e.g. some adverse effect guidance)	NA		NA	3	C
Clinical practice information (expert opinion); inconsistent evidence	NA		NA	4	D

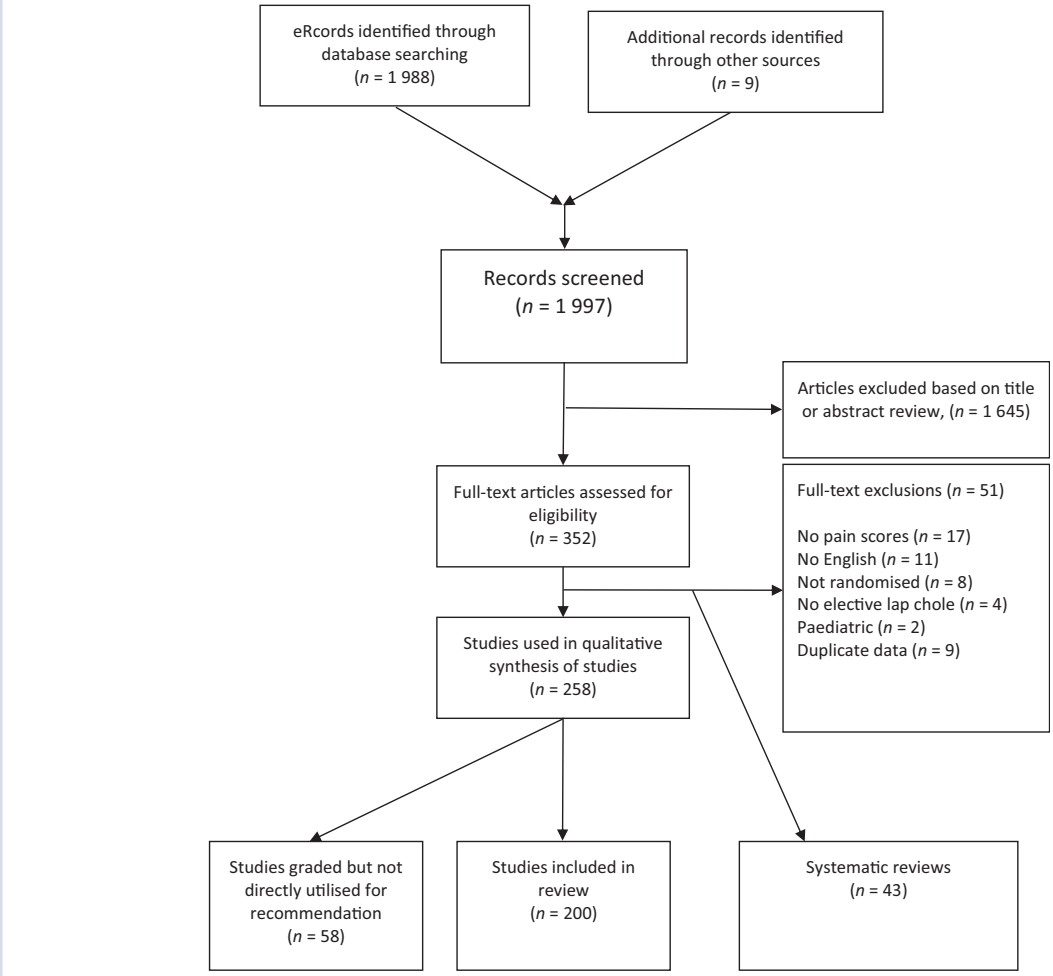

Fig 1. PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) diagram.

NSAIDs or COX-2 inhibitor

Before operation. The previous review recommended the use of NSAIDs (including COX-2 inhibitors) before operation (GRADE B). Seven papers examined the use of preoperative NSAIDs showing either reduced pain, analgesic requirement, or both (Table 3).[15–21] One paper compared showed no difference between preoperative i.v. paracetamol use *vs* ketorolac but had no control group.[22]

During operation. The previous review recommended the use of intraoperative NSAIDs (GRADE D). Two papers examined the use of intraoperative i.v. parecoxib, diclofenac, or dexketoprofen showing either reduced pain or analgesic requirement after operation (Table 3).[23,24]

After operation. One study examined the addition of dexketoprofen to a patient-controlled analgesia (PCA) showing reduced pain and opioid consumption (Table 3).[25] Another study showed lower rescue analgesic use with NSAID, but no change in pain scores.[26] One study showed no difference in pain scores or analgesic requirement if a single dose of parecoxib was given at the end of anaesthesia.[27] Two studies examined a combination of pre and postoperative NSAID showing reduced pain compared with placebo,[28] but the effect was not seen at small doses.[29]

Dexamethasone

The previous review recommended dexamethasone use with GRADE B evidence. Seven studies have examined the effect of preoperative dexamethasone. All showed effectiveness for up to 48 h after operation.[30–36] Furthermore, five of those studies have demonstrated a significant reduction in rates of nausea and vomiting.[30–33,36]

Dexamethasone with rofecoxib, ondansetron, and metoclopramide reduced the highest pain felt ($P=0.032$) and pain on arrival to ward ($P=0.03$).[37] The extent of the effect is unknown as the control group did not receive postoperative NSAID.

Wound local anaesthetic

The previous review recommended use of local anaesthetic (LA) into the wound. Infiltration of wound with ropivacaine was superior to placebo in reducing pain up to 24 h and

Table 2 Quality assessment and level of evidence assigned to randomised controlled trial included in the review. LoE, level of evidence

Quality score		LoE	References
Allocation concealment	Jadad score		
A	5	1	10,11,15,18,19,22,26–28,33,34,40,41,44,58,59,65,66,68–70,80,82, 84,91,99,101,102,104,105,107–109,117,125,130,131,138,143–145, 147–149,152,153,157,165,166,169,180,193,197,202,207,210
A	4	1	20,61,64,72,77,112,126,129,146,151,160,164,167,172,184
A	3	1	32,47,53,76,81,86,97,98,110,137,175–177,179,191,195,196
A	2	1	87,132,150,159
A	1	1	162
B	5	1	45,75,120,128,133,141,174
B	4	1	12,54,71,78,79,116,119,124,134,136,139,140,192,198
B	3	1	17,52,85,96,115,122,135,161,178,199–201,206
B	2	2	74,88,93,118,170,181,182,203,205
B	1	2	25
B	0	2	187
C	5	2	94
C	4	2	127
C	3	2	30,31,36,90,113,188,204
C	2	2	56,89,95,100,111,142
C	1	2	106
D	5	2	158
D	4	2	16,39,43,190
D	3	2	13,14,21,24,35,37,46,49,60,63,67,121,154,156,163,173,185,186,189
D	2	2	9,23,38,48,50,51,155,171,183
D	1	2	57,73,80
D	0	2	55,62

analgesic requirement.[38] Matkap and colleagues[39] compared local tramadol infiltration into wounds *vs* i.v. tramadol and found no significant difference in pain but a reduction in the use of rescue analgesia with the local tramadol group.

Two studies have used wound LA in addition to intraperitoneal (i.p.) LA. One study showed a significant reduction in pain with the addition of wound LA to i.p. LA.[40] Another study compared placebo with either i.p. LA or wound LA demonstrating no difference in pain or analgesic requirements with either intervention.[41]

One study examined infusion of ropivacaine into the wound for 24 h. The ropivacaine group reported less pain during cough (P=0.044) in the PACU (P=0.017) and at 4 h after operation compared with placebo (P=0.038).[42]

Opioids as rescue

No new RCT examined the use of breakthrough analgesia *vs* placebo. Fentanyl *vs* oxycodone PCA did not demonstrate any difference in one study.[43] Oxycodone was more effective when given immediately after operation but tended to have more side-effects.[44] The studies have shown significant side-effect profiles, which are to be avoided if possible.

Surgical technique

Low pressure. Low pressure defined as <12 mm Hg was recommended in the previous review (GRADE A). This update found a further 13 studies.[45–57] Of the 13 studies found, nine studies showed lower pain scores in the low-pressure group. The other four studies showed no significant difference between the two groups. Five of the 13 studies showed a lower analgesic requirement in the low-pressure group.

Saline lavage and suction. Saline lavage followed by suction was recommended in the previous review GRADE A. This review found a further three studies.[58–60] One of the studies[59] demonstrated lower pain scores in the saline lavage group, and two studies[58,59] demonstrated lower analgesic requirements in the saline lavage group.

Aspiration of pneumoperitoneum gas. Aspiration of pneumoperitoneum gas was not recommended in the previous review based on GRADE D evidence. This review found three studies that looked at aspiration of pneumoperitoneum gas.[61–63] One study[61] showed lower pain scores at 6 h, 1 day, and 2 days. Another study[63] showed lower pain scores at 1 h and 1 day. However, this was only for shoulder pain, not abdominal pain. Both of these papers showed no difference in analgesia requirement. The third paper[62] showed lower pain scores at Day 1 and lower analgesic requirement.

Mini port. There was no recommendation in the previous review. Two studies have reviewed the use of different size ports.[64,65] One study[64] showed a 5 mm port and three 3 mm ports improve pain at 1 h and 1 week when compared with a 10 mm port and three 5 mm ports. The other study[65] looked at either a 10 mm umbilical port with 3× 5 mm ports or 3× 3 mm ports. It showed no significant difference in pain scores between the two groups.

Not recommended for routine use but may be considered if the 'basic' analgesic technique is not possible or inadequate

Preoperative gabapentinoids

Preoperative gabapentoids was shown to be effective in reducing pain scores in 10 studies.[66–75] Five studies were

Table 3 Influence of NSAIDs or COX-2 inhibitors on postoperative pain. COX-2, cyclooxygenase-2; NS, not significant; t.d., transdermal; *r*, pain score at rest; *m*, pain score at movement; PCA, patient-controlled analgesia

Study (author, year)	Mode/timing	No. in treatment/ control arm	Treatment in intervention/ control arms	Follow-up period	Effect on pain score (for different follow ups)	Effect on postoperative analgesic requirement
Sandhu and colleagues 2011[18]	Preoperative	60/59	1 h preoperative received Etoricoxib 120 mg plus diazepam/diazepam with placebo	1, 2, 3, 4, 5, 6, 10, 14, 18, 22, 26 h	↓ at 10 h (0.023), ↓ 14 h (0.045), ↓ 26 h (0.011), ↓ average (0.013)	↓ Paracetamol PRN (0.006)
Kocaayan and colleagues 2007[17]	Preoperative	29/28	Lornoxicam 16 mg i.v. preinduction/40 mg Tenoxicam i.v. pre-induction	0, 15, 30 min; 1, 2, 4, 6, 12, 24 h	↓ for Lornoxicam at 15 min, 1 h, 2 h, 4 h (<0.05). NS rest of time periods	↓ Morphine consumption within first 2 h but not after (<0.05)
Papadmia and colleagues 2007[16]	Preoperative	25/25/26	Parecoxib 40 mg i.v./ Lornoxicam 8 mg i.v./placebo	0, 6, 12 h	↓ at 12 h for *r* and *m* (<0.05). NS for 0 and 6 h. For either treatment groups compared with placebo	↓ (0.001) Dose of Meperidine
Puura and colleagues 2006[15]	Preoperative	24/25/23	Etoricoxib 120 mg/Etoricoxib 120 mg, and paracetamol 1 g/ placebo	1, 2, 4, 10, 20 h	NS for all time periods and groups	↓ Fentanyl use for both Etoricoxib groups (<0.05)
Medina-Vera and Novoa 2017[22]	Preoperative	49/49	I.V. Paracetamol/i.v. Ketorolac	1, 3, 6, 12, 18, 24 h	NS for all time periods and groups	NS
Ahiskalioglu and colleagues 2017[21]	Preoperative	32/33	I.V. Ibuprofen/placebo 30 min before operation	30 min, 1 h, 2 h, 4 h, 8 h, 12 h, and 24 h	↓ pain at all time periods (<0.001)	↓ Opioid requirement at 24 h (<0.001)
Ural and colleagues 2014[20]	Preoperative	30/30/30	P.O. 1 h preoperative Diclofenac/i.m. pre-incision/ t.d. patch 6 h preoperative	0, 15, 30, 60 min	All time periods (<0.001) less pain with i.d. or t.d. compared with p.o. I.M. *vs* t.d. is NS	P.O. group had higher Tramadol bolus requirement immediately after operation *P*<0.001
Shuying and colleagues 2014[19]	Preoperative	37/38/38	Paracoxib pre-induction by 30 −45 min/Paracoxib intraoperative once gallbladder removed/placebo only	0.5−24 h	Reduces pain for pre-induction compared with other two groups *P*<0.05. No absolutes stated	↓ Analgesic use in preoperative and placebo group (*P*<0.05)
Anil and colleagues 2016[23]	Intraoperative	30/30	I.V. Dexketoprofen Trometamol 50 mg/i.v. Diclofenac 75 mg 30 min before end of procedure	2, 4, 8, 12, 18, 24 h	NS for all time periods	↓ Morphine PCA use for 2 and 4 h (0.01); 8, 12, 18, and 24 h (0.001) for either NSAID groups
Lin and colleagues 2015[24]	Intraoperative	60/60/60	S.C. Bupivicaine/i.v. Parecoxib/ placebo	1, 2, 4, 8, 12, 24 h	↓ 1, 2, 4 h both intervention groups compared with placebo (<0.05). NS for 8, 12, 24 h	↓ Rescue analgesia for both intervention groups at 24 h (0.018)
Akaraviputh and colleagues 2009[29]	Pre-/postoperative	40/30	30 min pre-induction and 12 h after first dose of Parecoxib 20 mg infusion/saline placebo for control	3, 6, 9, 12, 15, 18, 21, 24 h	NS for all time periods	NS (*P*=0.0530)
Kouroukli and colleagues 2013[28]	Pre-/postoperative	36/36/36	Lornoxicam (L) 8 mg p.o./ Paracoxib (Pa) 40 mg i.v./ placebo (pl 30 min before operation, then at 12 and 24 h	20 min, 3 h, 6 h, 12 h, 18 h, 24 h	At *r* 20 min ↓ L (0.001) Pa (0.003). ↓ 3 h L (0.023) Pa NS. 6 h ↓L (0.023) ↓ Pa (0.033). 12 h ↓L (0.001) Pa NS. 18 h ↓ L (0.014) ↓ Pa 0.012. 24 h ↓ L (0.008) Pa NS. 20 min ↓ at *m* for L (*P*=0.006) and Pa (0.001). 3 h at m for L NS, ↓ Pa (0.003). 6 h L NS, ↓Pa (0.001), 12 h at *m* for L NS, Pa ↓ (0.004). 18 h NS for both. 24 h NS for both	↓ For L and Pa *P*<0.005. @ 20 min and 24 h, Meperidine requirement
Abdulla and colleagues 2012[26]	Postoperative	30/30/30/30	Placebo/Parecoxib/Metamizol/ paracetamol	PACU, 6, 12, 24 h	NS for all time periods	↓ Piritrimide consumption from Metamizol group only
Ekmekci and colleagues 2012[25]	Postoperative	20/20	Both groups had PCA with Tramadol 600 mg in saline. Intervention group had 100 mg Dexktoprofen Trometamol added to PCA	2, 4, 6, 12, 24 h	↓ 2 h (0.035), ↓ 4 h (0.018), ↓ 6 h (0.026), ↓ 12 h (0.028), ↓ 24 h (0.040)	↓ Total opioid consumptions (0.04); but additional analgesic NS
Puolakka and colleagues 2006[27]	Postoperative	21/40/20	Parecoxib 80 mg/Parecoxib 40 mg/placebo given at end of anaesthesia	1, 2, 4, 6, 8, 10, 20 h	NS for all time periods and groups	NS for fentanyl use

shown to have no significant difference between placebo and preoperative gabapentinoids.[76–80]

Intraoperative IP local anaesthetic instillation

Various i.p. LA were used, but bupivacaine was the most common. There were considerable differences in the methods of LA instillation including the location (sub-diaphragmatic, gallbladder bed, or both, and with or without wound infiltration) and timing (before or after the removal of the gallbladder) between the trials.

Overall, 43 new trials were analysed.[40,41,81–122] Twenty-six studies demonstrated reduced pain scores and 17 trials showed no significant difference. A recent Cochrane review[123] showed only a marginal effect from many poor-quality studies of IP LA. One paper[124] found an analgesic benefit of using ropivacaine over bupivacaine.

Transversus abdominis plane block

Three studies compared transversus abdominis plane (TAP) blocks with LA infiltration into the wounds. Two of those studies showed the superiority of TAP blocks[125,126] with one showing no difference.[127] Nine studies[128–136] have shown that TAP or oblique subcostal TAP (OSTAP) blocks decreased postoperative pain more than placebo or morphine alone. Six studies[137–142] showed no difference in pain scores of TAP blocks compared with placebo.

Not recommended for routine analgesia

Ketamine

The previous review did not recommend ketamine use before or during operation (GRADE D).

One paper examined the use of ketamine with and without diclofenac 20 min pre-induction showing that ketamine alone pre-induction was not superior to placebo but was effective in combination with diclofenac.[143] Comparison between the combination of preoperative gabapentin, ketamine, lornoxicam, and local ropivacaine and each of these drugs alone for pain after laparoscopic cholecystectomy showed no difference in outcome.[144]

Intraoperative ketamine reduced postoperative pain and opioid requirement in four studies.[145–148] Five other studies have shown no difference in postoperative pain with intraoperative ketamine infusion.[149–153] Only one of those studies showing no effect with ketamine demonstrated a reduction in opioid requirement.[152]

Magnesium

The previous review did not recommend magnesium use before or during operation GRADE D.

Two studies examined preoperative magnesium infusion—one showing a reduction in pain up to 24 h[154] and the other reduction for the first 3 h only.[155] Both showed reduction in analgesic requirement. Intraoperative magnesium showed reduced pain scores within the first 24 h when compared with placebo after operation in two studies ($P<0.05$). Both studies showed reduced postoperative opioid requirements.[156,157]

Alpha-2 agonist

Dexmedetomidine infusion before operation and 24 h after operation was inferior in pain relief to the infusion of i.v. paracetamol alone within the first 24 h.[13] Dexmedetomidine and clonidine administered before operation did not significantly reduce pain but a reduced analgesic requirement.[158]

Regional anaesthetic techniques

Agarwal and colleagues[159] examined the effect of the paravertebral block given before induction showing no difference in pain score but lower morphine requirement with the block. However, the study is difficult to interpret given that there was no mention if LA was used in the wounds. Another study compared pre- and postoperative paravertebral blocks showing lower analgesic requirement in the preoperative group but no difference in pain scores.[160]

Four studies compared TAP blocks with LA infiltration into the wounds. Two of those studies showed the superiority of TAP blocks[125,126] with two showing no difference.[127,140] Eight studies have demonstrated that TAP or OSTAP blocks have less postoperative pain than placebo or morphine alone.[128–135] Only one study showed no difference in pain, but there was a reduction in analgesic requirement compared with placebo.[137] One study showed the effectiveness of ultrasound (US)-guided field block in reducing pain and analgesic requirement.[161]

Two studies examined epidural *vs* general anaesthesia. The pain was less on discharge for the epidural group.[162,163]

Lidocaine infusion

Lidocaine infusion was not recommended in the last review (GRADE D). One study compared fentanyl with lidocaine *vs* fentanyl only at induction.[164] There was no change in pain scores; however, the analgesic requirement was higher for the fentanyl only group. Four studies examined the use of intra- and immediately perioperative lidocaine infusion, and all[165–167] but one[168] showed reduced postoperative pain scores.

Esmolol infusion

Intraoperative esmolol infusion did not affect postoperative pain but reduced fentanyl use.[152,169] One study showed reduced pain score and analgesic requirement with intraoperative esmolol.[170]

Single port surgical techniques

A single port surgical technique was not recommended in the last review. This review included 39 studies[64,171–208] with mixed results regarding pain. An analgesic benefit favouring the single port technique was demonstrated in 12 of the studies[64,104,172,183,185,192,195,198,200,202,207,208]; however, 24 studies[171,174,176,177,179–182,184,186,187,189–191,193,194,196,197,199,201,203–206] showed no significant difference between the two groups. Three studies[173,175,188] showed an analgesic benefit for the traditional laparoscopic cholecystectomy group. A few studies reported significantly longer operating time in the single port group. A meta-analysis[209] of 37 studies reviewed 10-time points for pain, and only found a significant difference

between the two techniques at 12 h. The review did not show any difference in analgesic requirement.

Warmed and humidified insufflation gas

Warmed CO_2 was not recommended in the last review (GRADE A). Humidified CO_2 was not recommended in the previous review (GRADE B). Only one study examined the combined use of warmed and humidified CO_2 showing improved pain scores at 6 h but no difference at Day 1 and no difference in analgesia requirement.[210]

Discussion

Recommendations were made by the PROSPECT Working Group by evaluating the evidence from systematic reviews and RCTs. The final choice of intervention was established by evaluating the efficacy of analgesia against risks or intervention. The GRADE for the recommendations was supplied as per the consensus statement.[211]

Preoperative use of oral paracetamol and NSAID or COX-2 inhibitor is recommended based on several studies in this and the previous review (GRADE A). If paracetamol or NSAID

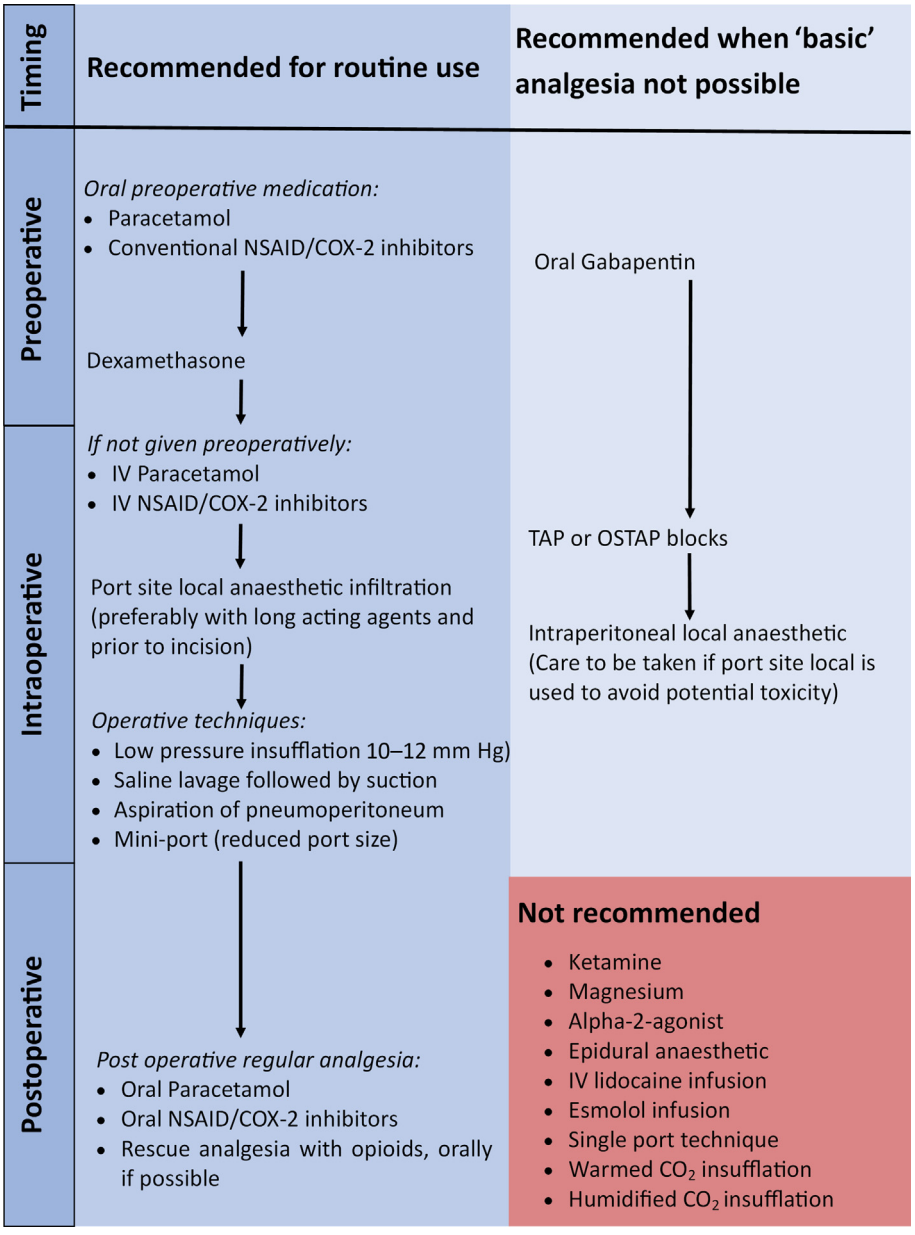

Fig 2. Updated PROSPECT (PROcedure SPECific Postoperative Pain ManagemenT) recommendations for pain management after laparoscopic cholecystectomy. COX-2, cyclooxygenase-2; TAP, transversus abdominis plane; OSTAP, oblique subcostal TAP.

was not administered before operation, then they can be given i.v. during operation (GRADES A and B, respectively). Paracetamol and NSAID are recommended to be continued after operation (GRADE A). The previous review recommended only postoperative paracetamol and NSAID, but this review extends this recommendation to the pre-/intraoperative period. Dexamethasone is recommended (GRADE A). Port site LA is recommended, preferably pre-incision with long-acting LA to prolong effect (GRADE A). Opioid analgesia should be reserved for rescue analgesia only (GRADE B).

Several surgical techniques are recommended to reduce postoperative pain. Low-pressure pneumoperitoneum (10–12 mm Hg) is recommended if surgically possible (GRADE A). Local lavage with saline and then suction is recommended after removal of the gallbladder (GRADE A). The lavage should be done with the adequate suction of remaining pneumoperitoneum (GRADE A). A mini-port laparoscopic technique is recommended as it reduces pain, but the cost and availability of equipment should be taken into consideration (GRADE B). Evidence for miniport is new to this review and not mentioned in the last review.

Preoperative gabapentinoids are not recommended for routine use but may be considered if 'basic' analgesia is not possible (GRADE D). Although several studies have reported reduced postoperative opioid requirements (LoE 1), it may not add to the effectiveness of 'basic' analgesic technique of paracetamol, NSAID, COX-2 inhibitors, and surgical site infiltration. Also, the optimal dose is unknown, and there is a need to balance analgesic benefits with potential adverse effects such as increased potential for sedation. Intraoperative i.p. LA instillation or TAP or OSTAP is not recommended (GRADE D). Although several studies have reported reduced postoperative opioid requirements and reduced pain scores (LoE 1), it may not add to the 'basic' analgesic protocol. The addition of i.p. LA with port site local infiltration could potentiate LA toxicity. The benefit of i.p. LA tends to be limited to the first few hours only when given during operation. If i.p. LA was to be used care should be taken to control the maximum dosage while still giving adequate port site LA.

Ketamine has shown mixed results regarding reduction of pain and analgesic requirement, and overall it is not recommended (GRADE D). Additionally, there are concerns about adverse effects such as hallucinations. Magnesium is not recommended despite some (LoE 1) evidence. Magnesium during operation may cause adverse effects such as potentiation of neuromuscular blocking agents and increasing the incidence of residual muscle paralysis. Alpha-2 agonists, such as dexmedetomidine, are not recommended because of limited evidence and potential adverse effects (GRADE D). Clonidine was recommended in the last review despite minimal evidence. This review did not recommend clonidine because of the ongoing limited evidence and potential side-effects. Regional anaesthesia techniques such as epidural analgesia, paravertebral block, intrathecal opioids, and rectus sheath block are not recommended because of limited small trial evidence and potential for complications or failure of anaesthetic technique (GRADE D). Epidural anaesthesia is counterintuitive in the ambulatory setting. Lidocaine or esmolol infusions are not recommended (GRADE D) despite the reduced pain in most studies owing to the need for close monitoring and the possibility of overdose.

There are several potential limitations to this review. This review depends entirely on the quality of available studies which are of mixed methodological quality (Table 2). The heterogeneity of included study methodologies precluded any useful meta-analyses of the available data. Many of the articles either did not state routine analgesic protocol or did not provide basic analgesia such as paracetamol or NSAID. Lack of routine analgesic protocol or inappropriate routine analgesia reduces the clinical relevance.

The recommended analgesic and surgical interventions for laparoscopic cholecystectomy are shown in Fig. 2. The recommendations for the various interventions are based on specific individual studies. Further studies are necessary to examine the effects of multimodal analgesia and test new interventions with adequate analgesia for the control group.

Authors' contributions

Design: A.B., W.M., A.H., G.J., PROSPECT group.
Literature search: A.B., W.M., J.R., S.T.
Analysis: A.B., W.M., J.R., S.T., A.H.
Interpretation of data: A.B., A.H., G.J., PROSPECT group.
Drafting of overall recommendations: PROSPECT group.
Literature search includes performing the search and data extraction and grading risk of bias for each article.

Declarations of interest

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