Pain management after laparoscopic hysterectomy: systematic review of literature and PROSPECT recommendations

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ABSTRACT

Background and objectives Laparoscopic hysterectomy is increasingly performed because it is associated with less postoperative pain and earlier recovery as compared with open abdominal hysterectomy. The aim of this systematic review was to evaluate the available literature regarding the management of pain after laparoscopic hysterectomy.

Strategy and selection criteria Randomized controlled trials evaluating postoperative pain after laparoscopic hysterectomy published between January 1996 and May 2018 were retrieved, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, from the EMBASE and MEDLINE databases and the Cochrane Register of Controlled Trials. Efficacy and adverse effects of analgesic techniques were assessed.

Results Of the 281 studies initially identified, 56 were included. Of these, 31 assessed analgesic or anesthetic interventions and 25 assessed surgical interventions. Acetaminophen, non-steroidal anti-inflammatory drugs, and dexamethasone reduced opioid consumption. Limited evidence hindered recommendations on alpha-2-agonists. Inconsistent evidence was found in the studies investigating pregabalin and transversus abdominis plane block, and no evidence was found for intraperitoneal local anesthetics, port site infiltration, or single-port laparoscopy. Measures to lower peritoneal insufflation pressure or humidify or heat insufflated gas seem to reduce the incidence of shoulder pain, but not abdominal pain.

Conclusions The baseline analgesic regimen for laparoscopic hysterectomy should include acetaminophen, a non-steroidal anti-inflammatory drug, dexamethasone, and opioids as rescue analgesics.

INTRODUCTION

Hysterectomy is one of the most common major surgical procedures performed in women. The laparoscopic approach is increasingly used, as it is associated with reduced postoperative pain and morbidity, as well as earlier recovery and a shorter hospital stay when compared with open hysterectomy.[1–5] However, pain may still be quite severe, particularly in the early postoperative period.[6 7] Literature assessing non-opioid pain therapy for patients undergoing vaginal and laparoscopic hysterectomy has been recently evaluated.[8] However, this study was not truly procedure-specific, including both vaginal and laparoscopic hysterectomies, and did not focus on opioid analgesics, anesthetics, and surgical technique.

The PROSPECT (PROcedure-SPECific postoperative pain managemenT) Working Group is a collaboration of anesthesiologists and surgeons which formulates evidence-based recommendations for postoperative pain management that are specific for different surgical procedures.[9 10] In addition to procedure-specific evidence, clinical practice information is used to provide overall recommendations considering the efficacy and adverse effects of an analgesic technique (www.postoppain.org).

The aim of this systematic review was to evaluate the available literature on the management of pain after laparoscopic hysterectomy. Postoperative pain outcomes (pain scores and analgesic requirements) were the primary focus, but other recovery outcomes, including adverse effects, were also assessed, when reported, and the limitations of the data were reviewed. The ultimate aim was to use the available evidence to develop recommendations for pain management in this patient population.

METHODS

A systematic review of randomized controlled trials (RCTs) published between January 1996 and May 2018 assessing analgesic interventions for laparoscopic hysterectomy was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines using EMBASE, PubMed, and the Cochrane Register of Controlled Trials.[11] The search terms related to pain interventions for laparoscopic hysterectomy surgery without language restriction included "laparoscopic hysterectomy" AND ("postoperative pain" OR "analgesia" OR "visual analog score" OR "local anesthetic" OR "regional anesthesia" OR "regional analgesia" OR "infiltration" OR "TAP block" OR "nonsteroidal antiinflammatory drugs" OR "non opioid analgesic" OR "opioid" OR "dexamethasone" OR "gabapentin" OR "pregabalin" OR "ketamine" OR "paracetamol" OR "acetaminophen" OR "corticosteroids"). We also manually retrieved publications referred in studies identified by our preceding search.

Study inclusion/exclusion criteria

We included RCTs assessing analgesic, anesthetic, or surgical interventions for laparoscopic hysterectomy with pain intensity measured by Visual Analog

Scale (VAS) or Numerical Rating Scale (NRS). Studies that did not measure pain intensity and studies including laparoscopic hysterectomy that reported data pooled with other surgical procedures were excluded. Three authors (JT, PL, and M-PB) conducted the literature search, while four authors (JT, M-PB, PL, and FB) were involved in the review of the literature search and exclusion of irrelevant articles where ambiguous. The results of the literature search were grouped according to analgesic modality and presented to the entire Working Group (see list of Authors) in two subsequent meetings half a year apart. The authors proposed interpretations of the findings, and the entire group was engaged in the drafting of the final recommendations in several iterations, collating rounds of individual comments on the evidence and draft recommendations, followed by round-table discussions and further rounds of individual comments. When consensus had been obtained, the lead authors compiled the manuscript, and again all the Working Group members participated actively in the writing and discussion. The methodology of the PROSPECT group is unique in that it aims to synthesize clinical evidence while considering the risks and benefits of interventions as well as taking into account study design. Specifically, the group seeks to determine the relevance of study interventions in current perioperative care practice and critically evaluate the baseline pain treatment. Recommendations are given when at least two congruent studies support an intervention.

Quality of included studies

The following were the criteria used to assess the quality of eligible studies: statistical analyses and patient follow-up assessment—indication whether statistical analysis was reported and whether follow-up was more or less than 80% of the patients; and allocation concealment assessment—indication whether there was adequate guarantee of blinding for treatment assignment (A, adequate; B, unclear; C, inadequate; D, not used; tables 1 and 2).[12] Quality of studies was graded using the Jadad Numerical Score (total 1–5) using the criteria based on appropriate randomization, double-blinding, and statements of possible withdrawals.[13]

Analysis of outcome and statistical analysis

We focused on pain intensity whenever it was the primary or secondary outcome. Unless specified otherwise, it was assumed that the pain scores were assessed at rest. We also retrieved comparative opioid consumption, particularly when the study design included patient-controlled intravenous opioid (morphine or morphine equivalent) administration. The studies were stratified according to the intervention evaluated: analgesic, anesthetic, or surgical. The effectiveness of each intervention was evaluated qualitatively by assessing the number of studies showing a significant difference. For the purpose of this review, we define a change >10 mm on a 100 mm VAS as clinically important.[14]

RESULTS

A total of 281 studies assessing analgesic interventions for laparoscopic hysterectomy were identified (figure 1). Of these, 23 retrospective studies, 31 non-randomized prospective, and 153 other publications were excluded. Of the remaining 74 RCTs, 18 studies were excluded (9 studies did not provide reproducible evaluation of pain, 2 studies expressed the results in figures and data could not be validated, and 7 studies did not provide data specifically for laparoscopic hysterectomy as data were pooled with other surgical procedures). Thus, 56 RCTs were included, 31 concerning analgesic or anesthetic treatments, and 25 concerning surgical procedures (figure 1).

The quality scores of all the studies reviewed (allocation concealment, Jadad score, and level of evidence) are reported in table 2, while details on analgesic interventions are given in table 3. For the qualitative analysis, the included trials were

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Table 1 Relationship between study quality and source of evidence, LoE, and grades of recommendation

| Study type | Study quality assessments | | | | | LoE | Grade of recommendation (based on overall LoE, considering balance of clinical practice information and evidence) |
	Statistical analyses and patient follow-up assessment		Allocation concealment*	Jadad scores	Additional assessment of overall study quality required to judge LoE		
Systematic review with homogeneous results	NA		NA	NA	NA	1	A
RCT	Statistics reported and >80% follow-up	AND	A	(1–5)	NA	1	A (based on two or more studies or a single, large, well-designed study)
		OR	B	(3–5)	NA		
		OR	B	(1–2)	Yes		
RCT	Statistics not reported or questionable or <80% follow-up	AND/OR	B	(1–2)	Yes	2	B (or extrapolation from one procedure-specific LoE 1 study)
		OR	C	(1–5)	NA		
		OR	D	1–5)	NA		
Non-systematic review, cohort study, case study (eg, adverse effects)	NA		NA			3	C
Clinical practice information (expert opinion); inconsistent evidence	NA		NA			4	D

*Allocation concealment is given as A adequate, B unclear, C inadequate, and D not used.
LoE, level of evidence; NA, not applicable; RCT, randomized controlled trial.

Table 2 Quality assessment and level of evidence assigned to the randomized trials included in this review

Study (reference number)	Statistics reported	Follow-up >80%	Allocation concealment	Jadad score	Level of evidence
Jokela et al[15]	Y	Y	A	5	1
Kim et al[16]	Y	Y	A	4	1
Kim et al[17]	Y	Y	B	4	1
Moon et al[18]	Y	Y	A	5	1
Jokela et al[19]	Y	Y	A	5	1
Thangaswamy et al[20]	Y	Y	A	5	1
Nam and Yoon[21]	Y	Y	B	1	2
Jokela et al[22]	Y	Y	A	5	1
Asgari et al[23]	Y	Y	A	5	1
Kim et al[24]	Y	Y	A	5	1
Jung et al[25]	Y	Y	A	4	1
Choi et al[26]	Y	Y	A	4	1
Lenz et al[27]	Y	Y	A	4	1
Kim et al[28]	Y	Y	A	3	1
Kim et al[29]	Y	Y	A	5	1
Park et al[30]	Y	Y	A	4	1
Lee et al[31]	Y	Y	B	3	1
Lee et al[32]	Y	Y	A	5	1
Hong and Lim[33]	Y	Y	A	5	1
De Oliveira et al[34]	Y	Y	A	4	1
Kane et al[35]	Y	Y	A	4	1
Calle et al[36]	Y	Y	A	5	1
El Hachem et al[37]	Y	Y	A	5	1
Torup et al[38]	Y	Y	A	5	1
Hutchins et al[39]	Y	Y	A	5	1
Ghisi et al[40]	Y	Y	B	3	1
Guardabassi et al[41]	Y	Y	B	3	1
Arden et al[42]	Y	Y	A	5	1
Andrews et al[43]	Y	Y	A	5	1
Barron et al[44]	Y	Y	A	5	1
Nelskyla et al[45]	Y	Y	A	2	1
Pokkinen et al[46]	Y	Y	B	3	1
Kim et al[47]	Y	Y	A	4	1
Muzii et al[48]	Y	Y	A	3	1
Song et al[49]	Y	Y	A	5	1
Eggemann et al[50]	Y	Y	A	5	1
Chen et al[51]	Y	Y	A	3	1
Li et al[52]	Y	Y	A	2	1
Jung et al[53]	Y	Y	A	2	1
Chung et al[54]	Y	Y	D	3	2
Kim et al[55]	Y	Y	D	3	2
Song et al[56]	Y	Y	D	3	2
Fanfani et al[57]	Y	Y	B	3	2
Paraiso et al[58]	Y	Y	A	5	1
Sarlos et al[59]	Y	Y	A	3	1

Continued

Table 2 Continued

Study (reference number)	Statistics reported	Follow-up >80%	Allocation concealment	Jadad score	Level of evidence
Tchartchian et al[60]	Y	N	B	1	2
Ghezzi et al[61]	Y	Y	A	5	1
Acton et al[62]	Y	Y	D	3	2
Shen et al[63]	Y	Y	A	3	1
Bogani et al[64]	Y	Y	A	5	1
Madsen et al[65]	Y	Y	A	5	1
Herrmann and De Wilde[66]	Y	Y	A	5	1
Radosa et al[67]	Y	Y	B	3	2
Roy et al[68]	Y	Y	A	2	1
Fagotti et al[69]	Y	Y	A	5	1
Rothmund et al[70]	Y	Y	B	2	2

Statistics reported andFollow-up >80% information is given as Y for Yes and N for No. Allocation concealment is given as A adequate, B unclear, C inadequateand D not used. Jadad score is numerical from 1-5.

divided into three groups—analgesic interventions, anesthetic interventions, and surgical procedures.

Analgesic interventions
Systemic non-opioid analgesics
Acetaminophen and *non-steroidal* anti-inflammatory drugs
In a three-arm study, the analgesic effects of acetaminophen/ondansetron, acetaminophen/placebo, or placebo/placebo were investigated. The cumulative 24-hour dose of the rescue analgesic, oxycodone, was lower in patients receiving acetaminophen, but not influenced by ondansetron. Pain scores and opioid side effects were not different between groups.[15] The efficacy of bupivacaine port site infiltration and ketorolac administration was compared in a four-arm study, where the lowest pain scores during the first 6 hours following surgery were found in the group which received both port site infiltration and ketorolac versus placebo.[16] Further, another study compared intravenous patient-controlled analgesia (PCA) using remifentanil, two combinations of remifentanil and ketorolac, and fentanyl combined with ketorolac. Ketorolac had a sparing effect on remifentanil consumption and decreased sedation score by, on average, approximately 0.5 points.[17]

Moon and colleagues[18] investigated the opioid-sparing effects of either 200 mg or 400 mg nefopam when added to a fentanyl intravenous PCA over the first 48 postoperative hours. Cumulative on-demand fentanyl consumption during the first 48 hours postoperatively was $236 \pm 128 \mu g$ vs $107 \pm 105 \mu g$ for the fentanyl-only versus the fentanyl-nefopam group, while pain scores, side effects, and patient satisfaction were not different.[18]

In summary, administration of non-opioid drugs such as acetaminophen, ketorolac, or nefopam has an opioid-sparing effect, but effects on mobilization and opioid-related side effects are unclear. Even though not powered to detect such an outcome variation, neither of the studies using non-opioids reported excessive bleeding in the non-steroidal anti-inflammatory drug (NSAID) groups.

Steroids
The potential analgesic efficacy of dexamethasone was tested in a four-arm study comparing three doses of dexamethasone
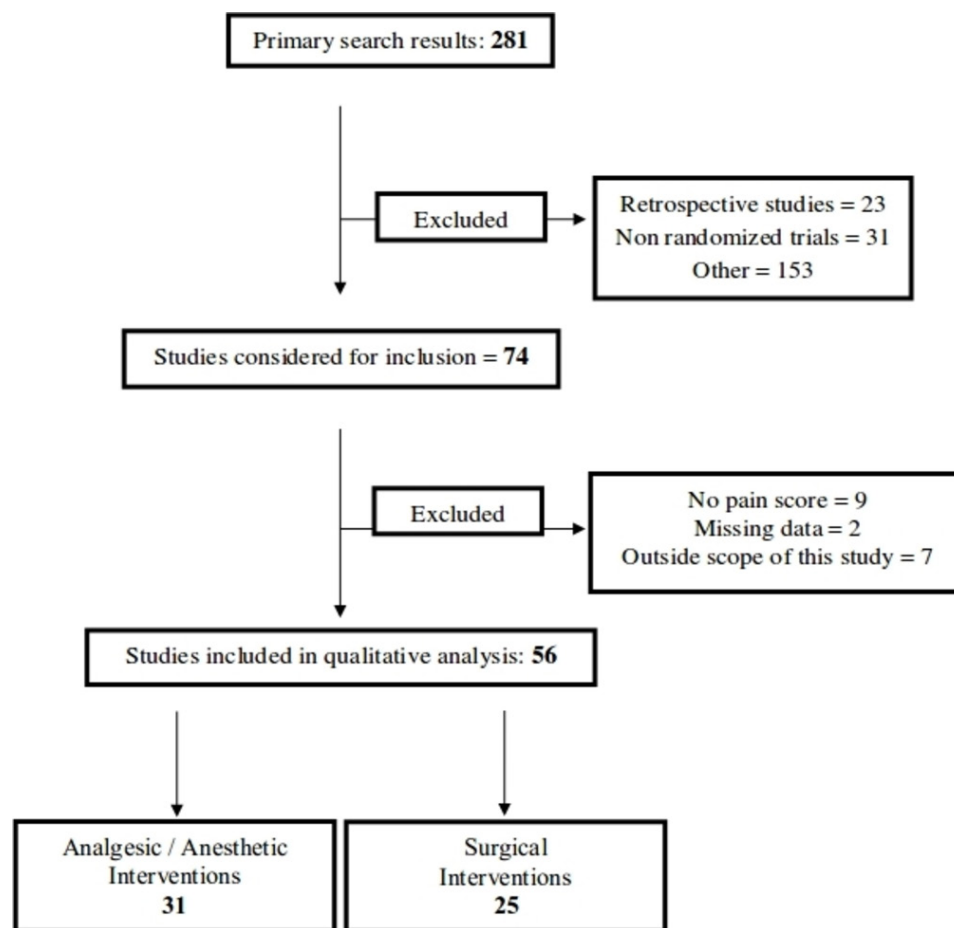
Figure 1 PRISMA flow chart of literature search. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

(15 mg, 10 mg, and 5 mg, intravenously) with placebo, administered before induction of anesthesia.[19] During the first 24 hours postoperatively, cumulative oxycodone dose was lower in the 15 mg dexamethasone (0.34 [range 0.11–0.87] mg/kg) group as compared with placebo (0.55 [range 0.19–1.13] mg/kg), and during the first 2 hours postoperatively oxycodone consumption in the 10 mg group was also lower. At the same time, resting and dynamic VAS scores as well as side effects (including sedation) were comparable.[19] Another study compared dexamethasone 4 mg or 8 mg administered 2 hours before induction of anesthesia with placebo.[20] All patients received acetaminophen and ibuprofen as baseline analgesics. Pain scores were not different, but cumulative postoperative fentanyl demand during the first 24 hours was less in the dexamethasone 8 mg group (547±69 μg) compared with the placebo (646±77 μg) and dexamethasone 4 mg groups. Postoperative nausea and vomiting (PONV) were significantly less frequent in the dexamethasone 8 mg group. No adverse effects related to dexamethasone were observed.[20] Further, dexamethasone 10 mg plus ondansetron was compared with ondansetron only, with no differences in the two groups in the mean VAS scores and mean opioid consumption, but the rate of PONV was lower in the group receiving both drugs.[21]

In summary, dexamethasone seems to exhibit dose-dependent opioid-sparing effects and contributes to reducing PONV, but does not reduce pain scores.

Gabapentinoids

The pre-emptive analgesic effect of two doses of pregabalin (300 mg and 600 mg) or diazepam (10 mg) was compared in a three-arm study, with the medications given as premedication and after 12 hours.[22] Only opioids were administered on the day of surgery. The VAS scores for pain at rest, on movement, and on coughing were comparable in the three study groups. The cumulative dose of oxycodone (0–24 hours after surgery) was lower in the pregabalin 600 mg group as compared with the diazepam group, but patients receiving pregabalin suffered from side effects such as dizziness, blurred vision, and headaches more frequently. Asgari and colleagues[23] randomized 96 patients to two preoperative and one postoperative dose of pregabalin 75, 150, or 300 mg, or placebo (n=24 each). The authors found that both 150 mg and 300 mg of pregabalin decreased pain scores, but in the 300 mg group the sedation score was significantly higher than in the placebo and the lower dosed groups.[23] Curiously, not a single patient in the pregabalin 300 mg and the placebo group required any rescue opioids despite the fact that no standardized multimodal regimen was used. In conclusion, pregabalin has potential opioid-sparing effects, but especially at higher doses it may be associated with side effects precluding its widespread use.

Alpha-2 adrenergic agonists

Kim and colleagues[24] investigated the effects of different doses of dexmedetomidine on postoperative shivering. In patients receiving 1 μg/kg body weight of dexmedetomidine, time to rescue analgesic was prolonged by, on average, 11 min as compared with placebo, and the number of patients requiring rescue analgesics in the postanesthesia care unit (PACU) (93% of control patients) was reduced to 50% and 43% in patients

Table 3 Summary of key results from studies evaluating systemic analgesics, analgesics adjuncts, regional anesthesia, and surgical procedures in patients undergoing LH

Study	Study design/adequate baseline analgesia	Pain scores	Cumulative opioid doses
Baseline analgesia (systemic non-opioids)			
Jokela et al[15]	Acetaminophen 1 g/ondansetron every 6 hours (n=40), acetaminophen/placebo (n=40) and placebo/placebo (n=40).	NS	Rescue opioid oxycodone lower in acetaminophen group (0.34±0.15 vs 0.43±0.18 mg/kg).
Kim et al[16]	Ketorolac intramuscularly + bupivacaine infiltration (n=21), ketorolac intramuscularly/placebo (n=20), bupivacaine/placebo (n=21), placebo/placebo (n=21).	Lower in the ketorolac bupivacaine group by 1–1.7 NRS points.	Lower in ketorolac bupivacaine group vs placebo.
Kim et al[17]	Intravenous PCA remifentanil (n=20), intravenous PCA remifentanil + ketorolac (2 doses, n=19 and n=20), intravenous PCA fentanyl (n=20).	NS	Lower in patients with ketorolac.
Moon et al[18]	Fentanyl PCA with nefopam 2 or 4 mg (n=28 and 26) per PCA bolus or fentanyl only (n=27).	NS	Lower in both nefopam groups.
Analgesic adjuncts			
Jokela et al[19]	3 intravenous doses of dexamethasone 15 mg, 10 mg, and 5 mg, 30 patients in each group. Baseline analgesia: acetaminophen and ibuprofen from POD 1.	NS	Lower in dexamethasone 10 mg and 15 mg doses.
Thangaswamy et al[20]	Intravenous 4 mg (n=18) and 8 mg (n=19) dexamethasone vs placebo (n=18). Baseline analgesia: acetaminophen and ibuprofen after discharge to ward.	NS	Lower for the 8 mg dexamethasone dose vs placebo.
Nam et al[21]	Dexamethasone 10 mg + ondansetron (n=25) vs ondansetron (n=25). Baseline analgesia: not reported.	NS	NS
Jokela et al[22]	2 doses of pregabalin (300 mg, n=31; 600 mg, n=30) vs diazepam (n=30). Baseline analgesia: acetaminophen and ibuprofen from POD 1.	NS	Oxycodone rescue lower for the 600 mg pregabalin dose (0.09±0.07 mg/kg) vs diazepam (0.15±0.13 mg/kg).
Asgari et al[23]	3 doses of pregabalin (75, 150, or 300 mg, n=24 each). Baseline analgesia: diclofenac or pethidine on request.	Lower in the 150 and 300 mg groups by between 1.5 and 3 NRS points.	No patient in placebo or 300 mg group received rescue opioids.
Kim et al[24]	Bolus dexmedetomidine at end of surgery: placebo, 0.5, 0.75, or 1 µg/kg (n=30 each). Baseline analgesia: Not reported.		Less likely to require rescue analgesic (0.75 and 1 µg/kg groups).
Jung et al[25]	Continuous intravenous infusion of dexmedetomidine (n=25) vs remifentanil (n=25). Baseline analgesia: ketorolac.	NS	
Choi et al[26]	Brief intravenous infusion of dexmedetomidine (n=30) vs remifentanil (n=25) vs fentanyl (n=30). Baseline analgesia: ketorolac.	NS	
Regional anesthesia			
Hong and Lim[33]	Epidural analgesia started before incision (n=25, pre-emptive) vs epidural started after surgery (n=25). Baseline analgesia: no.	Lower in pre-emptive epidural group by 2–3 NRS points between 3 and 12 hours postoperatively.	Lower in pre-emptive epidural group.
De Oliveira et al[34]	Preincisional 20 mL infiltration TAP block with ropivacaine (0.5%, n=22; and 0.25%, n=21) vs saline (n=23). Baseline analgesia: acetaminophen, ketorolac, ibuprofen.	Lower in ropivacaine groups by 1–3 NRS points on the first POD.	Lower in ropivacaine 5 mg/mL group.
Kane SM, 2012[35]	Postoperative 20 mL infiltration TAP block with 0.5% ropivacaine (n=28) vs no block (n=29). Baseline analgesia: ketorolac single shot at end of surgery.	NS	NS
Calle et al[36]	Postoperative 40 mL infiltration TAP block with 1.5 mg/kg body weight bupivacaine (n=100) vs placebo block (n=97). Baseline analgesia: acetaminophen, ketorolac.	Lower at discharge in TAP group (less than 1 NRS point).	NS
El Hachem et al[37]	Postoperative 30 mL ultrasound-guided or laparoscopically guided TAP block using 0.25% mg/mL bupivacaine vs trocar infiltration (n=88, each patient as own control). Baseline analgesia: acetaminophen, ketorolac.	NS	NS
Torup et al[38]	Preincisional 40 mL ultrasound-guided TAP block using ropivacaine 0.5% (n=34) vs placebo (n=31). Baseline analgesia: acetaminophen, ketorolac.	NS	NS
Hutchins et al[39]	Preincisional 30 mL bupivacaine 0.25% subcostal TAP block (n=30) vs 30 mL 1.3% liposomal bupivacaine (n=28). Baseline analgesia: acetaminophen, ibuprofen.	Worst pain score lower by 2.5 NRS points during the first 24 hours and 2 NRS points during 24–48 hours in liposomal group.	Lower during the first 24 hours and until 48 hours in the liposomal group.

Table 3 Continued

Study	Study design/adequate baseline analgesia	Pain scores	Cumulative opioid doses
Ghisi et al[40]	Preincisional 40 mL levobupivacaine 0.375% (n=22) vs no block (n=22), combined with systemic analgesia. Baseline analgesia: opioid only.	NS	NS
Guardabassi et al[41]	Postoperative opioid PCA plus TAP block (n=20) vs opioid PCA (n=20).	NS	NS
Intraperitoneal local anesthetics			
Arden et al[42]	Intraperitoneal bupivacaine infiltration (n=67) vs placebo (n=73). Baseline analgesia: ketorolac, acetaminophen.	NS	NS
Andrews et al[43]	Continuous intraperitoneal bupivacaine infusion (n=30) vs placebo (n=30). Baseline analgesia: non-standardized mix of NSAID, acetaminophen, opioids.	NS	NS
Port site infiltration			
Kim et al[16]	See above.	Lower in the ketorolac bupivacaine group by 1–1.7 NRS points.	Lower in ketorolac bupivacaine group vs placebo.
El Hachem et al[37]	See above.	NS	NS
Barron et al[44]	Bupivacaine 0.25% vs liposomal bupivacaine (n=30 each). No standardized multimodal baseline medication.	Worst pain improved in liposomal group on POD 2 and 3 by 1.5–2 NRS points.	NS
Anesthetic techniques			
Nelskyla et al[45]	Maintenance with isoflurane (n=30) vs propofol (n=30). Baseline analgesia: ketoprofen.	NS	NS
Pokkinen et al[46]	Maintenance with sevoflurane (n=74) vs propofol (n=74). Baseline analgesia: acetaminophen.	NS	NS
Kim et al[47]	Single bolus propofol (0.5 or 1 mg/kg) or placebo (n=33, 34, and 40). Baseline analgesia: ketorolac in PCA.	NS	NS
Surgical techniques			
Muzii et al[48]	LAVH (n=40) vs MLH (n=41). Baseline analgesia: not standardized.	Lower in LAVH group by 1.5–2 NRS points on POD 1 and 2.	
Song et al[49]	TLH (n=38) vs LAVH (n=38). Baseline analgesia: not standardized.	Lower in TLH by 1 NRS point 18 hours after surgery.	NS
Eggemann et al[50]	Vaginal hysterectomy vs LAVH, with or without peritoneal closure (n=47–50 each).	Lower in vaginal hysterectomy by less than 1 NRS point.	NS
Chen et al[51]	Single-port LAVH (n=50) vs the conventional multiport LAVH (n=52). Baseline analgesia: intramuscular pain medicine on request.	Lower in the single-port group by 1–1.5 NRS points at 24 and 48 hours.	Lower in the single-port group.
Li et al[52]	Single-port LAVH (n=52) vs conventional LAVH (n=56). Baseline analgesia: not reported.	NS	
Jung et al[53]	Single-port LAVH (n=30) vs 4-port LAVH (n=34). Baseline analgesia: tamiflumate, intramuscular ketorolac or meperidine on request.	NS	NS
Chung et al[54]	Single-port (n=30) vs conventional laparoscopy (n=30). Baseline analgesia: PCA and tramadol.	NS	NS but higher incidence of rescue analgesics in the single-port group.
Kim et al[55]	Single-port (n=122) vs conventional laparoscopy (n=121). Baseline analgesia: not reported.	NS	NS
Song et al[56]	Single-port (n=20) vs conventional laparoscopy (n=21). Baseline analgesia: ketorolac in PCA, zaltoprofen orally.	NS	NS
Fanfani et al[57]	Single-port hysterectomy (n=34) vs miniport laparoscopy (n=34). Baseline analgesia: intravenous acetaminophen on demand.	Lower in miniport group by 1–1.5 NRS points until 8 hours postoperatively.	Opioids not reported but rescue analgesics not different.
Paraiso et al[58]	Conventional (n=27) vs robotic-assisted (n=26) laparoscopy. Baseline analgesia: not reported.	NS	NS
Sarlos et al[59]	Robotic vs conventional laparoscopic hysterectomy, (n=95). Baseline analgesia: not reported.	NS	NS
Tchartchian et al[60]	Laparoscopic-assisted combined (n=14) vs LAV hysterectomy (n=12). Baseline analgesia: detailed scheme including metamizole, opioid PCA.	NS	NS
Ghezzi et al[61]	MLH (n=38) vs LH (n=38). Baseline analgesia: ketorolac, acetaminophen.	NS	NS
Acton et al[62]	Laparoscopy using 5 mm (n=36) or 10 mm (n=40) laparoscope. Baseline analgesia: acetaminophen, celecoxib.	Less pain by approximately 1 NRS point in the 5 mm group.	

Table 3 Continued

Study	Study design/adequate baseline analgesia	Pain scores	Cumulative opioid doses
Shen et al[63]	Drain (n=80) vs no drain (n=84). Baseline analgesia: not reported.	Lower for shoulder tip pain.	Lower in the drain group.
Bogani et al[64]	Low-pressure (n=20) vs standard-pressure (n=22) laparoscopy. Baseline analgesia: acetaminophen, ketorolac on demand.	Abdominal pain similar, shoulder tip pain lower in low-pressure group.	Rescue analgesics NS.
Madsen et al[65]	Laparoscopy with deep neuromuscular blockade and low pressure (n=49) or standard pressure (n=50). Baseline: acetaminophen, etodolac.	Abdominal pain similar, incidence of shoulder tip pain lower in low-pressure group.	NS
Herrmann and De Wilde[66]	Laparoscopy using humidified and heated CO_2 (n=48) or controls (n=49). Baseline analgesia: metamizole.	NS	Higher in control group
Radosa et al[67]	Active CO_2 elimination (n=98), CO_2 elimination plus trocar site infiltration (n=95), or control (n=96). Baseline analgesia: metamizole.	Higher in the control group by 0.5–1.7 NRS points at 3, 24, and 48 hours.	Higher piritramide requirement in the control group during the first 24 hours.
Roy et al[68]	TLH (n=30) vs LAVH (n=30), vs non-descent vaginal hysterectomy (n=30). Baseline analgesia: not reported.	NS	
Fagotti et al[69]	Thunderbeat electrosurgery or conventional cautery (n=25 patient per group). Baseline analgesia: acetaminophen.	Lower pain scores by 1–1.5 NRS points mm in the Thunderbeat group.	More patients requiring rescue analgesics in the conventional group.
Rothmund et al[70]	Standard bipolar (n=80) vs EnSeal cautery (n=80). Baseline analgesia: not reported.	NS	

Empty fields denote variable not reported.

CO_2, carbon dioxide; LAVH, laparoscopic-assisted vaginal hysterectomy; LH, laparoscopic hysterectomy; MLH, minilaparoscopic hysterectomy; NRS, Numerical Rating Scale; NS, no significant difference between groups; NSAID, non-steroidal anti-inflammatory drug; PCA, patient-controlled analgesia; POD, postoperative day; TAP, transversus abdominis plane; TLH, total laparoscopic hysterectomy.

receiving 0.75 and 1 μg/kg body weight, respectively. A study compared intravenous infusions of dexmedetomidine/ketorolac (n=25) with remifentanil/ketorolac (n=25) administered from the end of surgery to the arrival in the PACU.[25] The early VAS scores were not significantly different between the two groups until 30 min after PACU arrival, when the study ended. In conclusion, there are insufficient data to form a recommendation for dexmedetomidine. When Choi and colleagues[26] compared different brief analgesic infusions at the end of surgery, they found no difference in pain scores or analgesic side effects between remifentanil, fentanyl, and dexmedetomidine.

Opioids

Several studies compared different variations of opioids in their ability to control pain. These studies compared intravenous PCA morphine versus oxycodone,[27] fentanyl versus oxycodone,[28–30] and brief infusions of remifentanil[31] or sufentanil[32] before extubation. There is insufficient evidence to specifically recommend one opioid over another. Observational studies suggest that most patients after laparoscopic hysterectomy require opioids as rescue drugs, for a median of 4 days.[6]

Regional anesthesia/analgesia

Epidural analgesia

The pre-emptive analgesic effects of epidural analgesia were compared with epidural analgesia started after skin closure in patients with cervical cancer scheduled for laparoscopic hysterectomy. Continuous epidural analgesia using a patient-controlled epidural analgesia (PCEA, lidocaine and morphine) was continued for 72 hours. In the pre-emptive epidural analgesia group, pain scores and rescue PCEA opioid consumption were lower, and side effects nausea, vomiting, and pruritus were reduced, as compared with epidural analgesia initiated after the end of surgery.[33] During surgery, after the initial top-up in the pre-emptive group, blood pressure was slightly lower than baseline, while in the group that had not received an epidural bolus blood pressure was higher than baseline. The overall recovery effect of this 72-hour regimen compared with other simple multimodal opioid-sparing techniques was not determined. Patients in the pre-emptive epidural group had median pain scores of less than 4 after surgery and less than 3 at 3 hours postoperatively, whereas the control group reached similar pain control only between 12 and 24 hours after surgery.

Transversus abdominis plane block

The efficacy of ultrasound-guided transversus abdominis plane (TAP) block was assessed in several studies. De Oliveira and coworkers[34] compared two concentrations of ropivacaine (5 mg/mL or 2.5 mg/mL) with saline for TAP block and found lower NRS pain scores in the ropivacaine groups by 2–3 points in the PACU, and at 24 hours, and in addition lower opioid consumption in the 5 mg/mL ropivacaine group as compared with saline (7.5 vs 15 mg morphine equivalent). Importantly, this study used standard multimodal analgesia (opioid, acetaminophen, ibuprofen) in all patients.

When comparing TAP block with no block, Kane and colleagues[35] found no differences in pain scores or opioid requirements. In this study, intraoperative and postoperative titration of analgesics was at the discretion of the treating doctors, and all patients received NSAID. Calle and colleagues[36] compared TAP block with placebo in the setting of ambulatory laparoscopic hysterectomy and found a lower VAS score at discharge in the TAP group (by less than 1 point on the NRS), which was statistically but not clinically relevant, while no difference was observed at 12 or 24 hours when patients received a standard baseline analgesic regimen including ibuprofen and acetaminophen. Of note, the TAP block in this study was performed using the loss-of-resistance technique without ultrasound, under laparoscopic vision.

In another study, when compared with trocar site infiltration in the setting of multimodal analgesia, single-shot ultrasound-guided TAP block decreased neither pain scores to a clinically significant extent (mean difference less than 1 point on the NRS), nor intraoperative or postoperative opioid use or antiemetic prescription.[37] Torup and colleagues[38] investigated the use of TAP block when added to multimodal analgesia (two non-opioids, morphine PCA) and found no additional benefit concerning pain scores when compared with placebo blocks, no reduction in opioid use, and no difference in adverse events. Hutchins and colleagues[39] investigated the use of liposomal bupivacaine compared with plain bupivacaine for subcostal TAP block in patients undergoing robotic-assisted laparoscopic hysterectomy. There was no clinically significant difference in median maximal pain scores in the immediate postoperative period, but the liposomal bupivacaine group had decreased maximum pain scores, decreased opioid use, and a lower incidence of PONV for the first 24 hours.[39] Ghisi and coworkers[40] compared ultrasound-guided TAP block with systemic opioid analgesia and found no advantage in terms of VAS score, opioid consumption, postoperative mobilization, or adverse events. Finally, Guardabassi and colleagues[41] found no advantage in terms of opioid consumption during the first 24 hours, and no difference in pain scores, when TAP blocks were added to a systemic analgesia regimen including opioid PCA.

Intraperitoneal local anesthetics

Two studies investigating different regimens of local anesthetics used for intraperitoneal instillation of local anesthetics demonstrated no clinically relevant benefit. Arden and coworkers[42] compared the instillation of local anesthetic in the pelvic region, but not the trocar insertion sites, with saline placebo and found no difference in VAS scores or adverse events. Andrews and colleagues[43] investigated continuous intraperitoneal infusion of 5 mg/mL levobupivacaine at 2 mL/hour for 48 hours as compared with saline placebo, and found higher postoperative analgesic requests in the levobupivacaine group while attaining comparable pain scores.

Port site infiltration

As indicated above, the efficacy of bupivacaine port site infiltration and ketorolac administration was compared in a four-arm study, where the lowest pain scores during the first 6 hours following surgery were found in the group which received both port site infiltration and ketorolac.[16] Also, in the setting of multimodal analgesia, patients receiving trocar site infiltration reported the same (low) pain scores as patients receiving single-shot ultrasound-guided TAP blocks.[37] Barron and colleagues[44] showed that port site infiltration with liposomal bupivacaine, when compared with plain bupivacaine, showed lower pain scores on postoperative days 2 and 3, with no difference in opioid consumption, psychometrics, or analgesic side effects. In summary, based on one well-designed study, epidural analgesia started before skin incision provided adequate analgesia postoperatively. TAP blocks were less effective, with four out of seven studies negative, two studies positive on the margin of clinical significance, and one positive study. Liposomal bupivacaine for TAP block, in one study, seemed to have a prolonged effect, and lowered worst pain scores during first 24 hours, as well as opioid consumption. Intraperitoneal local anesthetic infusion showed no analgesic benefits in the setting of laparoscopic hysterectomy. There is no procedure-specific evidence for port site infiltration.

Anesthetic interventions

In a study comparing isoflurane and propofol for maintenance of general anesthesia, pain scores and postoperative analgesic requirements were comparable in the two groups,[45] and in a similar study no difference was found when anesthesia was maintained with sevoflurane versus propofol.[46] Finally, a single antiemetic dose of propofol at the end of surgery did not influence pain scores or opioid requirements.[47]

Surgical interventions

Surgical techniques are chosen based on anatomic and patient-centered factors, with postoperative pain scores playing a lesser role. Laparoscopic-assisted vaginal hysterectomy (LAVH) was shown in one study to lead to less pain compared with minilaparotomy,[48] while the difference in a second study was minimal.[49] Eggemann and colleagues[50] found only minor differences in pain (less than 1 point on the NRS) when vaginal hysterectomy was compared with LAVH. Studies comparing single-port surgery versus minilaparotomy were mixed, with one study reporting less pain in the single-port group,[51] while others finding no difference.[52 53] Chung and colleagues[54] reported more rescue analgesics in the single-port group when it was compared with a standard three-port surgery while other studies found no difference in pain scores or analgesics.[55 56] Compared with single-port hysterectomy, minilaparoscopy led to lower pain scores in one study.[57] No difference in pain scores and analgesics was found when robotic and conventional laparoscopic hysterectomy were compared.[58 59] Laparoscopic combined hysterectomy was not different from conventional hysterectomy.[60] Minilaparoscopy compared with conventional (larger-bore) hysterectomy led to no[61] or only minimal[62] decreases in pain scores.

Pneumoperitoneum, drains, and cautery

A study compared closed suction (Jackson-Pratt) drains with no drains.[63] Shoulder tip, abdominal, and back pain were evaluated by measuring VAS scores at 3 hours, 24 hours, and 48 hours after surgery. Closed suction drains reduced shoulder tip pain at 24 hours. At 48 hours, fewer women who received drains experienced abdominal pain. There were no statistically significant differences in VAS scores for back pain at any time point. The oral analgesics demand was higher in patients with no drain.

Pain after pneumoperitoneum was investigated by several studies. Bogani and colleagues[64] compared low-pressure (8 mm Hg) versus standard-pressure (12 mm Hg) pneumoperitoneum and found that while abdominal pain was similar between groups, the incidence of shoulder tip pain in the early postoperative period was 36% in the standard and 5% in the low-pressure group. Madsen and colleagues[65] demonstrated less shoulder tip pain with lower inflation pressure. When carbon dioxide (CO_2) was humidified and heated, postoperative shoulder tip pain scores, but not abdominal pain scores, were lower than when using control gases.[66] Lastly, elimination of CO_2 with an open umbilical trocar decreased postoperative pain scores, but additional trocar site infiltration did not decrease pain scores or opioid consumption further.[67] In one study, there were no differences in postoperative pain and adverse events between total laparoscopic hysterectomy, LAVH, and non-descent vaginal hysterectomy.[68]

Fagotti and colleagues[69] compared postoperative pain and operative time when using conventional laparoscopic cautery, or a combined multifunctional instrument (Thunderbeat, Olympus, Tokyo, Japan), and found a shorter surgery time, but only small differences in postoperative pain. Similarly, no difference in

postoperative pain scores was found when an EnSeal (Ethicon, Norderstedt, Germany) was compared with conventional bipolar coagulation.[70]

In summary, limited data suggest that small-port laparoscopy may decrease early and short-term postoperative pain, and low inflation pressure or humidified and heated CO_2 may decrease shoulder tip pain, but not abdominal pain.

DISCUSSION

This systematic review examined the effects of analgesic, anesthetic, and surgical techniques on postoperative pain after laparoscopic hysterectomy.

Based on the available studies, non-opioids (acetaminophen and NSAIDs) have opioid-sparing effects, but in the procedure-specific studies they did not reduce opioid side effects. The number of patients included was too small to draw valid conclusions concerning their safety profile in the settings of laparoscopic hysterectomy. The combination of port site infiltration and NSAID resulted in a better analgesia than either technique alone in one small study[16] and showed equivalence to TAP blocks in another.[37] Based on the origin and the type and duration of pain after laparoscopic hysterectomy, as well as the available evidence from procedure-specific RCTs, it is recommended to administer acetaminophen and NSAID combination to all patients unless there are contraindications. The studies supporting the opioid-sparing effect were of generally good quality, but study size was small in all but one study.[15] This approach is supported by a recent network meta-analysis on patients after major surgery.[71]

Dexamethasone was shown to reduce opioids in two studies which were of higher quality,[19 20] while one study with lower quality[21] found no effect. Effective doses seemed to be in the range of 8–10 mg. Even though the timing of dexamethasone administration has not been specifically investigated in the setting of laparoscopic hysterectomy, evidence from visceral abdominal surgery suggests that early administration after anesthetic induction may offer the best antiemetic,[72] anti-inflammatory, and analgesic effects.[73]

Pregabalin was found in two well-designed trials[22 23] to be opioid-sparing, but specific side effects (blurred vision, dizziness) were also increased. It should be noted, however, that the doses used were rather high (up to 600 mg). More evidence is needed to determine the potential beneficial effects of alpha-2-agonists, despite promising results in one trial.[24]

Evidence on epidural analgesia was limited, while evidence on TAP blocks was inconsistent, and that for intraperitoneal local anesthetics was negative. Epidural analgesia provides excellent pain relief for patients undergoing laparoscopic hysterectomy, but given the fact that surgery is now often performed on an ambulatory basis, and the adequacy of less invasive modalities in managing pain in most patients, it is performed very rarely[74] and should be considered a reserve intervention. Several studies evaluated the use of TAP blocks for laparoscopic hysterectomy; however, the results are conflicting. When added to non-opioids and opioids, or compared with a simpler procedure such as port site infiltration,[37] TAP block failed to consistently yield clinically significant benefits. Quality of studies did not seem to differentiate between positive and negative outcomes. One potential reason for the failure of TAP blocks in some trials may be the localization of port sites; depending on the size of the uterus and pathology, these may be placed at the level of and below the umbilicus, or above the umbilicus, and as mentioned others may use midline single-port techniques.[35] So lateral TAP blocks may not be optimally suited for all types of laparoscopic

hysterectomy, and subcostal blocks may be more appropriate for patients with more cranial port insertion points. There was also heterogeneity in block performance; some blocks were performed before surgery, while some others were performed after skin closure, and Hutchins and colleagues[39] used liposomal bupivacaine. There were not enough studies to differentiate further whether any particular variant of TAP block might be more effective than others, such that a universal recommendation cannot be given at this point.

Intraperitoneal instillation of local anesthetic provided no clinically significant benefit in two studies with good quality and adequate sample size.[42 43] At the present time, there is no procedure-specific evidence of benefit of port site infiltration for laparoscopic hysterectomy, although we note that significant benefit has been demonstrated for this intervention for laparoscopic cholecystectomy.[75]

Analgesics adjuncts which have been suggested as potential options include ketamine and intravenous lidocaine infusion. These approaches are not recommended for laparoscopic hysterectomy because of inadequate procedure-specific evidence. In addition, the benefit of adding these drugs to the recommended pain management regimen (box 1) has not been evaluated.

General anesthesia is the standard of care for laparoscopic hysterectomy, and from an acute pain standpoint the choice of maintenance anesthetics has no detectable effect on postoperative pain, such that the main determinants for choosing the maintenance anesthetic agents are patient-related, such as cardiovascular comorbidity and the risk of PONV.

With respect to the surgical technique, limited data suggest that minilaparoscopy may lead to lower postoperative pain scores. Measures to lower peritoneal insufflation pressure or humidify or heat insufflated gas may help to reduce the incidence of shoulder tip, but not abdominal, pain.

All these considerations need to be taken into account with the timeline of patients moving through the perioperative period. Between 2005 and 2013, the incidence of laparoscopic hysterectomy increased from less than 20% to account for more than two-thirds of all hysterectomies in the USA.[76] When divided by subgroup, the largest increase was observed in robotic-assisted laparoscopic hysterectomy, while the number of single-port laparoscopic surgeries was negligible.[76] The overall initial postoperative pain can be severe,[7] but generally subsides to NRS scores <4 within 1 day.[77] Pain generated from laparoscopic hysterectomy includes incisional pain, which can be severe initially, but subsides within the first half day; visceral pain, which takes longer (up to a day) to resolve; and shoulder pain, which is milder, typically

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Box 1 Overall recommendations for pain management in patients undergoing laparoscopic hysterectomy

Perioperative interventions in time to secure analgesia in immediate postoperative period.
► Acetaminophen.
► Non-selective NSAID or COX-2 selective inhibitor.
► Single dose of dexamethasone, intravenously.

Postoperative period.
► Acetaminophen (paracetamol) and NSAID or COX-2 selective inhibitor.
► Rescue opioid.

COX, cyclo-oxygenase; NSAID, non-steroidal anti-inflammatory drug.

appears within 24 hours and can last for several days.[7] Typical length for use of opioid rescue drugs is approximately 4 days in a recent US study.[6] Laparoscopic hysterectomies are increasingly performed as ambulatory procedures,[78] emphasizing the need for standardized pain management on discharge. In this light, continuous or invasive methods such as epidural analgesia and intravenous opioid PCA may not be suited for prospective ambulatory patients and should be regarded reserve interventions. Lastly, as mentioned above, robotic surgery is increasingly used to perform laparoscopic hysterectomy,[79] but the two studies investigating pain scores found no advantage in terms of pain as such over conventional laparoscopic hysterectomy.[58 59]

Our study confirms and expands on the results of a prior systematic review focusing on non-opioid analgesics.[8] Similar to this study, we found opioid-sparing effects of non-opioids such as acetaminophen, NSAIDs, and dexamethasone, and ambivalent evidence for regional techniques. We respectfully disagree with the authors of this systematic review[8] on the risk-benefit analysis of anticonvulsants, the opioid-sparing effects of which need to be weighed against increased risk of sedative side effects.

Strengths

The strength of our systematic review comes from the interpretation of the individual pieces of literature according to a predetermined methodology of the PROSPECT Working Group, with an interdisciplinary Delphi process to achieve consensus.[9 80] This approach goes beyond a simple summation of results and seeks to interpret on the basis of background/baseline analgesic technique, side effects, and clinical context.

Limitations

The limitations of this study are related to the limitations of the included studies. Most of the included studies assessed "unimodal" analgesic therapies rather than broader and more comprehensive analgesic techniques. Ideally, control groups should receive an optimized analgesic regimen, and the added procedure-specific benefit of specific interventions should then be tested against this backdrop.[81] Also, there was significant heterogeneity in study designs with respect to the analgesic regimen. The minimal clinically important difference (MCID) in pain score has been debated, and while some have suggested a cut-off of 20 mm on a 100 mm VAS, or 30% on the NRS,[82] some have argued for 10 mm[14] and others have advocated individualizing MCID to baseline pain.[83] We chose 10 mm as our defined MCID in accordance with the recent study by Myles and colleagues,[14] who postulated 10 mm to be the MCID, and an absolute score of 33 mm on a 100 mm VAS to signify "acceptable pain control." Although most studies report pain at rest, studies reporting pain on activity would be more suited to judge recovery from surgery with respect to mobilization.

Future outlook

The primary outcome measures for systematic reviews by the PROSPECT Working Group are pain and opioid consumption. Although these parameters have been used in clinical research for the past decades, future studies and systematic reviews need to link these measures of pain with more far-reaching outcome parameters, such as mobilization, length of hospital stay, the incidence of complications, and the occurrence of chronic pain or chronic opioid consumption. Summarizing these considerations, we often do not use the most effective method to treat pain (eg, combined femoral and sciatic nerve blocks for knee arthroplasty),[84] but the one we consider most appropriate after weighing risks and benefits.[85] The present recommendations take this into account by suggesting a framework of basic analgesic interventions, supplemented by rescue medications, that can serve as a gold standard which can readily be implemented and against the backdrop of which future interventions need to be tested.[10] Also, as individualized treatment plans seek to take into account patient-specific factors such as chronic pain,[6] or pre-existing opioid therapy,[86] our recommendations can serve as the common basis from which to tailor and adapt analgesic plans.

CONCLUSIONS

In summary, although considered less painful than open abdominal hysterectomy, laparoscopic hysterectomy requires standardized postoperative pain management, particularly in the early postoperative period. The PROSPECT recommendations provide clinicians with supporting arguments for and against the use of analgesic interventions for laparoscopic hysterectomy (table 3). A balance of the analgesic efficacy and potential risks of the analgesic intervention determines these recommendations. Perioperative pain treatment for laparoscopic hysterectomy should include, unless contraindicated, acetaminophen and an NSAID continued into the postoperative period primarily for their ability to reduce opioid use, dexamethasone for its ability to decrease analgesic use and act as an antiemetic, and opioids as rescue postoperatively.

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