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Intraperitoneal local anesthetics for postoperative pain management following intra-abdominal surgery: a systematic review and meta-analysis

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Abstract

Importance Although intraperitoneal local anesthetics are commonly used following intra-abdominal surgical procedures, the level of evidence supporting their use for postoperative pain management remains uncertain.

Objective To evaluate the effect of intraperitoneal local anesthetics on postoperative pain following intra-abdominal surgery.

Data sources Medline (PubMed), Embase (Embase.com), CENTRAL, Web of science and ClinicalTrials.gov databases were searched from their inception to July 15th, 2022.

Trial selection Randomized controlled trials comparing IPLA to placebo, usual care or other analgesic regimens among patients of any age undergoing any type of surgery.

Data extraction and synthesis Trial selection, data extraction, risk of bias assessment and the certainty of evidence were conducted in duplicate independently. Meta-analyses were performed using random effect models.

Main outcomes and measures The co-primary outcomes were abdominal pain intensity at 6, 12, 24, 48, and 72 h after surgery. Secondary outcomes included postoperative nausea and vomiting, opioid use, recovery of gastrointestinal transit, length of hospital stay, postoperative chronic pain, persistent postoperative opioid use, quality of recovery and adverse events.

Results A total of 150 trials ($n=11,821$ participants were included in our systematic review (97% of trials among adults). Intraperitoneal local anesthetics reduced postoperative pain intensity at 6 h (-0.86 point [95%CI -1.02 to -0.70]), 12 h (-0.74 point [95%CI -0.93 to -0.55]), 24 h (-0.65 point [95%CI -0.82 to -0.48]), and 48 h (-0.51 point [95%CI -0.70 to -0.31]), but not at 72 h (-0.38 point [95%CI -1.04 to 0.27]), with very low to low certainty of evidence. Modelled

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risk difference for achieving the clinically important effect and subgroup analyses among participants with moderate or high pain showed potential clinically significant effect from IPLA. Opioid use at 24 h (-10.4 mg of oral morphine equivalent [95% CI -13.1 to -7.6]), postoperative nausea and vomiting (RR 0.79 [95% CI -0.71 to 0.88]), and time to gastrointestinal transit recovery (-3.80 h [95% CI -7.54 to -0.07]) were also reduced. We found no association for other outcomes.

Conclusion and relevance Intraperitoneal local anesthetics may be associated with a small analgesic effect following intra-abdominal surgery. Considering the low to very low level of evidence supporting these findings, along with the limited data on adverse effects and long-term outcomes, their adoption as a standard of care intervention cannot be recommended at this stage.

Registration number CRD42018115062.

Keywords Systematic review, Meta-analysis, Surgery, Intraperitoneal anesthesia, Local anesthetics

Introduction

Local anesthetics are commonly used for perioperative pain management in perioperative care, whether for local infiltration, neuraxial analgesia or intravenous infusion [1–3]. Over the last decade, the administration of local anesthetics (using instillation, irrigation or nebulization) directly into the peritoneal cavity has gained popularity with the development of laparoscopic intra-abdominal surgery, providing minimally invasive access to the peritonealcavity.

Recommendations to inform the perioperative use of intraperitoneal local anesthetics (IPLA) are inconsistent. Based on the Enhanced Recovery After Surgery (ERAS) Society, IPLA is a promising technique and a potential alternative to peridural analgesic [4, 5]. Nevertheless, the National Institute for Health and Care Excellence (NICE), the European Society for Paediatric Anaesthesiology (ESPA), and the American Pain Society do not recommend its use [6–8]. Systematic reviews carried out to date were restricted to a specific type of surgery, mostly laparoscopic cholecystectomy, [9–15] limiting the generalizability of results [16]. Most reviews showed a small short-term opioid-reducing effect, but the impact of IPLA on postoperative pain intensity remains unclear, as the clinical significance of the findings were rarely considered.

Our systematic review and meta-analysis of randomized controlled trials aimed to evaluate the effectiveness of the perioperative administration of IPLA in patients undergoing intra-abdominal surgery [17, 18].

Methods

Study design

The protocol for this systematic review and meta-analysis was registered in PROSPERO (*CRD42018115062)*. It was conducted following the Cochrane Handbook for Systematic Reviews methodology [19] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines [20]. Human Research Ethics and Consent to Participate were not applicable, since the data used are in the public domain.

Search strategy

The search strategy, validated according to the Peer Review of Electronic Search Strategies (PRESS) guidelines, [21]. was developed by clinical experts (surgeons and anesthesiologists), method experts in systematic reviews, and information specialists. We searched for relevant citations through Medline (Pubmed), Embase (Embase.com), Cochrane Central Register of Controlled Trials and Web of Science from their inception to July 15th, 2022. An example of the search strategies is available in online-only material (eAppendix). ClinicalTrials.gov database was searched for protocols and unpublished trials.

Eligibility criteria

Randomized controlled trials comparing IPLA to placebo, no intervention, other analgesic regimen, or usual care in patients of any age undergoing any type of intra-abdominal surgery (laparoscopy or laparotomy), regardless of the type of anesthesia, were considered for inclusion. All types of IPLA were considered except liposomal local anesthetics. Trials were excluded when the comparator was a systemic local anesthetic. Intraperitoneal co-interventions were accepted, but other types of combination of interventions were excluded. Full-text articles reporting at least one outcome measure of interest were considered. No language restriction was used.

Outcome measures

Our co-primary outcomes were patient reported postoperative abdominal pain intensity at 6, 12, 24, 48, and 72 h after surgery, regardless of the scale used [22]. Intervals considered for each time point were 0 to 6 h, 7 to 12 h, 13 to 24 h, 25 to 48 h, and 49 to 72 h, respectively. The latest time point available for each interval was extracted. When dynamic and rest pain intensity scores were reported, dynamic pain was prioritized and only

unidimensional instruments using a 10 or 100-point scale were considered [23]. Secondary outcomes included cumulative opioid equivalent administration (mg of oral morphine equivalent) at 24 h (0 h to 24 h interval) and 48 h (24 h to 48 h interval), incidence of nausea and vomiting, recovery of gastrointestinal transit (delay in hours), hospital length of stay (days), quality of recovery, [24] persistent postoperative opioid use, incidence of postoperative chronic pain, and incidence of adverse events: local anesthetic toxicity, urinary retention, respiratory depression, vagal reaction/bradycardia, anastomotic leak, surgical site infection, and serious adverse events.

Trial selection and data extraction

Pairs of six reviewers (MB, CM, MV, XS, HZ, MAG) independently screened trials for eligibility in duplicate. Disagreements were resolved by discussion or with the assistance of a third-party reviewer (AFT or SO). The data from included trials were collected independently in duplicate by pairs among seven reviewers (MB, CM, MV, XS, SO, HZ and MAG) using a standardized data extraction form. Extracted data included trial characteristics (title, authors, year of publication), participant and surgical procedure information (type of surgery, type of participants [adult vs. pediatric], number of participants randomized and analyzed), intervention details (agent used, volume, concentration, dose, method and timing of administration, presence of co-interventions, and presence of co-analgesia), comparator details and data regarding outcomes of interest in each group. Pain intensity scores were extracted when reported using a scale from 0 to 10 or 0 to 100 and converted into a score between 0 (no pain) and 10 (highest pain intensity imaginable) when necessary [23, 25]. Cumulative opioid administration quantities were converted in oral morphine equivalent as per the 2017 Canadian clinical practice guidelines for opioid therapy and chronic noncancer pain [26]. When continuous data were reported with a median and standard error or range, estimates were calculated using a validated tool [27]. Results provided in the form of graphs were extracted using *WebPlot Digitizer version 2.6.8* [28]. All articles not written in English, French or Spanish have been translated using the online translator *Google Translate (United States, Google LLC*, 2016) [29, 30].

Risk of Bias assessment

The risk of bias of trials was assessed independently in duplicate by pairs of reviewers (MB, CM, MV, XS, SO, FL, LB, HZ) using the *Cochrane Collaboration Risk of Bias Tool.*[31]. The overall risk of bias was based on the worst score obtained across the seven domains.

Statistical analyses

All meta-analyses were conducted using *Reviewer Manager Software version 5.4.1.* using the DerSimonian and Laird method with random effect models (inverse variance) [32]. The clinical significance of the analgesic effect was assessed considering the minimal clinically important difference (MCID) (1 point out of 10) [33–35]. We also calculated the risk difference between groups for achieving the MCID using the Hasselblad and Hedges method to convert continuous outcome measure into dichotomous outcome measure considering our skewed data distribution [36–39]. Dichotomous data were presented as risk ratios (RR) and presented with 95% CI. Zero total event trials were included in meta-analyses [40]. We also performed sensitivity analyses by excluding trials with an average post-operative pain score below or equal to 3/10 in the comparator group as per the Cochrane Pain, Palliative and Supportive Care Review Group recommendations [41].

The presence of statistical heterogeneity was assessed using the I^2 statistic (threshold for substantial heterogeneity: >50%). Clinical and methodological sources of heterogeneity were explored through planned subgroups analyses: the type of surgery (close vs. open vs. both), the class of IPLA used (long action [bupivacaine, levobupivacaine, ropivacaine], intermediate/short action [lignocaine, xylocaine, prilocaine] or mixed), the type of comparator (usual care vs. placebo vs. intraperitoneal active comparator vs. systemic active comparator), the method of administration (instillation or infusion vs. irrigation vs. nebulization or spraying vs. other vs. multiple methods) and timing of IPLA administration (beginning of procedure vs. toward the end of procedure vs. beginning and end of procedure vs. postoperative infusion), the presence of a co-intervention (intraperitoneal co-analgesia vs. no intraperitoneal co-analgesia), the risk of bias of the trials (low vs. high vs. unclear) and the nature of surgery (cholecystectomy, gynecological procedures, appendectomies, bariatric surgery, colorectal surgery, multiple surgeries or inguinal hernia) [42, 43]. Sources of heterogeneity were interpreted through visual inspection of subgroup forest plots as well as the overall and within subgroup I^2 statistic.

Certainty of evidence and trial sequential analyses

The certainty of the evidence was determined according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach using the GRADEpro Guideline Development Tool [44]. The risk of publication bias was assessed through visual inspection of funnel plots and Egger's regression test (2 tailed) when an outcome of interest was evaluated in more than 10 trials (threshold for asymmetry, $p < 0.1$) [45]. We performed trial sequential analyses on all outcomes, using

trials sequential analysis monitoring boundary with heterogeneity-adjusted information size and weighted information fraction. The O'Brien-Fleming alpha-spending boundary function was used to calculate the cumulative Z-score [46, 47]. Trial sequential analyses were conducted using 5% alpha and 80% power with two-tailed test.

Results

Trials selection

A total of 4,164 records were identified through five databases. After duplicate removal and screening titles and abstracts, 274 full-text articles were assessed for eligibility. Subsequently, among the 168 trials ($n = 12,975$) included in the systematic review, 150 trials ($n = 11,821$) could be included in the meta-analysis (Fig. 1).

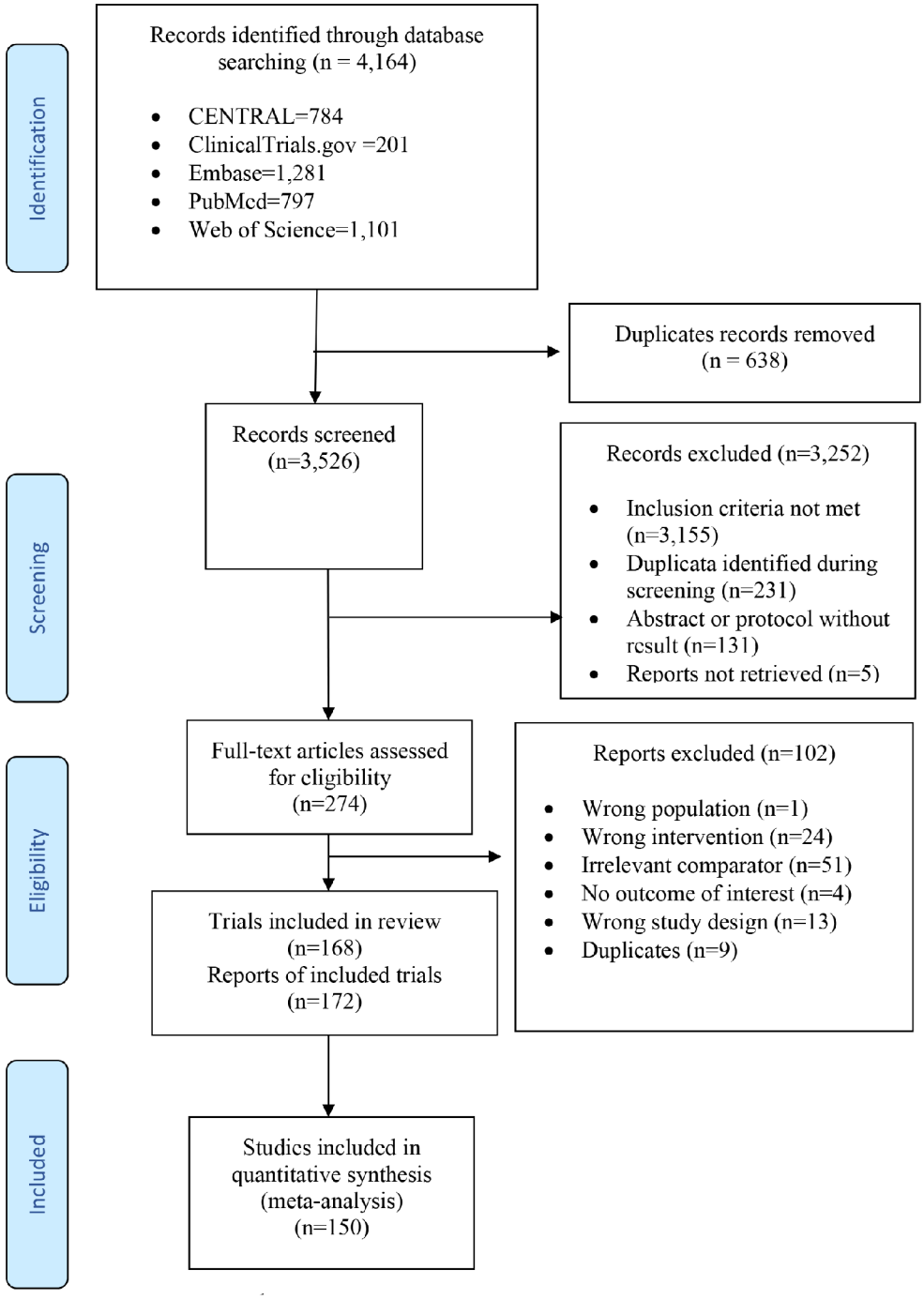

Fig. 1 Flow diagram of trials

Trials characteristics

Of the 150 trials included in the meta-analysis, 97% ($n = 145$) included adult patients only while others [48–52] only included pediatric patients. The surgical approach was opened in 7% of trials ($n = 11$), [50, 53–62] closed in 90% of trials ($n = 135$) and mixed in 3% of trials ($n = 4$). Most trials were conducted with general surgery patients (cholecystectomies, appendectomies, inguinal hernias) (56%, $n = 84$). In 98% of trials ($n = 147$), patients were under general anesthesia, while under spinal anesthesia in 2% ($n = 3$) [57, 60, 61]. In two trials, epidural analgesia was used for all participants [49, 63]. and for some participants in two other trials [64, 65]. Regional analgesia was not used in the other trials ($n = 146$). Most trials used long-acting anesthetic (88% of trials, $n = 132$). The type of comparator was a placebo in 81% of trials ($n = 121$), an active comparator administered in the peritoneal cavity in 5% of trials ($n = 8$), an active comparator administered intravenously in 5% of trials ($n = 8$), and usual care in 9% of trials ($n = 13$). An intra peritoneal co-interventions (epinephrine, opioid, dexmedetomidine, ondansetron, clonidine, magnesium or hydrocortisone) was used in 23% of the trials while none was used in 77% ($n = 116$) of the trials. The median patient follow-up duration was 24 h (eTable 1).

Risk of Bias

Of the 168 trials included in the systematic review, 7% ($n = 12$) were judged to be at low risk of bias, 58% ($n = 98$) were at unclear risk of bias, and 35% ($n = 58$) were at high risk of bias. The domain most frequently classified as being at high risk of bias was the blinding of intervention ($n = 24$) and attrition ($n = 24$) (eTable2, eFigure 1).

Postoperative pain intensity at 6, 12, 24, 48 and 72 h

Patient-reported abdominal postoperative pain intensity was evaluated in 166 trials with a dynamic pain assessment in 26% of them ($n = 43$), an assessment at rest in 8% ($n = 14$), and unspecified in 66% of trials ($n = 109$). A total of 120 trials could be included in the meta-analyses for pain assessment and mean pain scores in each group are provided in Table 1. Compared with control, IPLA reduced postoperative pain intensity (10-point scale) at 6 h (mean difference [MD], -0.86 point [95% CI -1.02 to -0.70], 112 trials [$n = 8,668$], low certainty of evidence), 12 h (MD, -0.74 point [95%CI -0.93 to -0.55], 88 trials [$n = 6,852$], low certainty of evidence), 24 h (MD, -0.65 point [95%CI -0.82 to -0.48], 103 trials [$n = 8,181$] low certainty of evidence), and 48 h (MD, -0.51 point [95%CI -0.70 to -0.31], 32 trials [$n = 2,272$], very low certainty of evidence), but not at 72 h (MD, -0.38 point [95%CI -1.04 to 0.27], 6 trials [$n = 387$], low certainty of evidence) (Table 1, eFigures 2–6). Modelled risk difference between groups for achieving the MCID showed a significant analgesic effect at 6, 12, 24 h and 48 h (Table 2). Results from subgroup analyses are presented in eFigures 7 to 10. There was an effect modification for the class of local anesthetic, and the type of comparator: (i) the analgesic effect was greater with the use of intermediate or short-acting local anesthetics compared to longer acting anesthetics for the 6 h, 12 h and 24 h time points; (ii) the analgesic effect from IPLA was greater when the comparator was placebo or no intervention. Based on the results of trial sequential analyses, the sample size of our meta-analyses for the 6, 12, 24, 48 h time points were larger than the required information size (eFigures 11 to 15). This was further suggested by the z-curve that crosses the trial sequential boundaries before the estimated required information size. After removing trials with pain scores ≤ 3/10 in the comparator groups, as a sensitivity analysis, the direction of effects was similar but with an increased magnitude of effects (eTable 3).

Postoperative opioid use at 24 and 48 h

Based on data from forty-one trials included in the meta-analysis, IPLA was associated with a decrease in postoperative opioid use at 24 h (MD, -10.35 mg of oral morphine equivalent [95% CI, -13.08 to -7.62 mg], 34 trials [$n = 2,935$], very low certainty of evidence), but not at 48 h (MD, -5.78 mg of oral morphine equivalent [95% CI, -11.98 to 0.42 mg], 10 trials [$n = 763$], very low certainty of evidence) (Table 1, eFigures 16–17). Effect on postoperative opioid use was smaller when IPLA was administered toward the end of the surgery (24 h time point), when nebulization or irrigation were used as methods of administration (24 h and 48 h time points), when the comparator was a placebo (24 h opioid use), when it was administered with a co-intervention in the peritoneal cavity (24 h time point), and when the risk of bias of the included trial was high (48 h time point) (eFigures 18–19). Based on trial sequential analyses, the sample size of the meta-analysis for the 24 h time point was larger than the required information size, while the 48 h time point was not (eFigures 20–21).

Postoperative nausea and/or vomiting and recovery of Gastrointestinal transit

The overall incidence of postoperative nausea and/or vomiting was 29% (1,674 events among 5,781 patients). The use of IPLA was associated with a reduction in nausea and vomiting (RR, 0.79 [95% CI, 0.71 to 0.88], 70 trials [$n = 5,781$], moderate certainty of evidence) (Table 1, eFigure 22). This finding was consistent across subgroup analyses (eFigure 23). Substantial subgroup differences were observed for the type of surgery and risk of bias, where perioperative use of IPLA was associated with less nausea and vomiting in trials with and open surgery and

Table 1 Summary estimates from Meta-analyses and certainty of the evidence assessment

Outcome Measure	Time-point	No. of Trials (*N* = 150)	No. of Participants (*N* = 11,821)	I^2, %	Intraperitoneal local anesthetics (Mean [SD] / Events)	Control (Mean [SD] / Events)	MD (95% CI) or RR (95% CI)	Egger test (*p*-value)	Certainty of Evidence
Postoperative Pain (10-point scale)[1]	6 h	112	8668	91%	2.7 [1.6]	3.6 [1.7]	-0.86 [-1.02 to -0.70]	0.92	⨁⨁◯◯ Low[a, b]
	12 h	88	6852	94%	2.6 [1.4]	3.4 [1.6]	-0.74 [-0.93 to -0.55]	0.22	⨁⨁◯◯ Low[a, b]
	24 h	103	8181	95%	2.3 [1.3]	3.0 [1.6]	-0.65 [-0.82 to -0.48]	0.62	⨁⨁◯◯ Low[a, b]
	48 h	32	2272	84%	1.9 [1.5]	2.5 [1.8]	-0.51 [-0.70 to -0.31]	0.02	⨁◯◯◯ Very Low[b, c,d]
	72 h	6	387	78%	1.5 [1.5]	2.2 [1.7]	-0.38 [-1.04 to 0.27]	-	⨁⨁◯◯ Low[e, f,g]
Opioid use (mg of oral morphine equivalent)[2]	24 h	34	2935	97%	33.4 [22.5]	42.2 [25.2]	-10.35 [-13.08, -7.62]	0.62	⨁◯◯◯ Very Low[a, h,i]
	48 h	10	763	80%	58.4 [26.7]	60.9 [30.0]	-5.78 [-11.98, 0.42]	0.02	⨁◯◯◯ Very Low[c, d,g, i,j]
Postoperative nausea and/or vomiting[3]	Median: 24 h	70	5781	38%	826/3209	848/2572	0.79 [0.71, 0.88]	0.47	⨁⨁⨁◯ Moderate[a]
Recovery of gastrointestinal transit (h) [3]		8	454	75%	37.7 [23.2]	44.8 [23.1]	-3.80 [-7.54, -0.07]	-	⨁⨁◯◯ Low[f, g,k]
Length of hospital stay (days)		28	2695	75%	2.5 [1.0]	2.6 [1.3]	-0.00 [-0.03, 0.03]	0.12	⨁⨁◯◯ Low[h, k]
Local Anesthetics Systemic Toxicity[3]	Median: 24 h	16	1228	N/A	3/684	1/544	2.74 [0.30, 25.40]	-	⨁⨁◯◯ Low[g, l]
Urinary retention[3]	Median: 24 h	7	736	33%	2/380	4/356	0.65 [0.07, 6.33]	-	⨁⨁◯◯ Low[g, l]
Respiratory depression[3]	Median: 24 h	10	786	N/A	0/407	0/379	Not estimable	-	-
Vagal Reaction/Bradycardia[3]	Median: 24 h	9	753	56%	12/435	4/318	1.69 [0.24, 12.08]	-	⨁◯◯◯ Very Low[g, l,n, o]
Anastomotic leak[3]	Median: 24 h	9	832	0%	7/438	4/394	1.34 [0.38, 4.70]	-	⨁◯◯◯ Very Low[g, l,m]

Table 1 (continued)

Outcome Measure	Time-point	No. of Trials (*N* = 150)	No. of Participants (*N* = 11,821)	I^2, %	Intraperitoneal local anesthetics (Mean [SD] / Events)	Control (Mean [SD] / Events)	MD (95% CI) or RR (95% CI)	Egger test (*p*-value)	Certainty of Evidence
Surgical site infection[3]	Median: 24 h	10	1056	0%	10/550	11/506	0.94 [0.42, 2.13]	-	⨁⨁◯◯ Low[g, l]
Serious adverse events[3]	Median: 24 h	9	967	0%	2/545	0/422	2.26 [0.24, 21.35]	-	⨁⨁◯◯ Low[g, l]

[1]Intervals considered for the time point: 6 h, 0 to 6 h; 12 h, 7 to 12 h; 24 h, 13 to 24 h; 48 h, 25 to 48 h; and 72 h, 49 to 72 h. [2]. Intervals considered for the time point: 24 h, 0 to 24 h; 48 h, 24 to 48 h. [3].Latest en time-point available was extracted

a. Most domains from studies are at unclear risk of bias. A large proportion of studies had no information on incomplete outcome data or are subject to attrition bias. Selective reporting could not be assessed in a large proportion of studies due to absence of protocol. Blinding of outcome assessed was at low or unclear risk of bias in most studies. The true estimate of effect is likely to be influenced by the risk of bias within and across studies

b. High statistical heterogeneity. However, most studies have the same direction of effect. High statistical heterogeneity remaining within subgroups

c. Most domains from studies are at unclear risk of bias. A large proportion of studies had no information on incomplete outcome data or are subject to attrition bias. Selective reporting could not be assessed in a large proportion of studies due to absence of protocol. Blinding of the intervention was at unclear or high risk of bias for most studies. Blinding of outcome assessed was at low or unclear risk of bias in most studies. Finally, studies with bigger weights in the meta-analysis were at unclear or high risk of bias. The true estimate of effect is likely to be influenced by the risk of bias within and across studies

d. Results from the Egger regression test suggest potential publication bias

e. Most domains from studies are at unclear risk of bias. Selective reporting was rated as unclear risk of bias due to absence of available protocol for a large number of studies. Studies with bigger weights in the meta-analyses were considered at high or unclear risk of rias. The true estimate of effect is likely to be influenced by the risk of bias within and across studies

f. High statistical heterogeneity. However, most studies have the same direction of effect

g. Required information size not reached in trial sequential analysis

h. High statistical heterogeneity. Substantial differences in the direction of effect among studies with smaller weights. Subgroup analyses does not explain heterogeneity (high statistical heterogeneity within subgroups)

i. Change in opioid use may be associated with adverse events or benefits from the intervention. It is an indirect measure of analgesia

j. High statistical heterogeneity. Substantial differences in the direction of effect among studies with smaller weights

k. Most domains from studies are at unclear or high risk of bias. Among studies with bigger weights in the meta-analyses, studies were subjected to attrition bias and selective reporting (absence of protocol). Studies with bigger weights in the meta-analysis were at unclear risk of bias. The true estimate of effect is likely to be influenced by the risk of bias within and across studies

l. Low number of events and participants, resulting in large confidence intervals

m. Risk of attrition bias and allocation concealment among studies with events

n. Most domains are at unclear risk of bias

o. High statistical heterogeneity and differences in the direction of effects

CI: Confidence intervals; MD: Mean difference; RR: relative risk

Table 2 Risk difference for achieving the minimal clinically important difference in postoperative pain intensity

Time-Point	No. of Trials	No. of Participants	Risk Difference for Achieving the MCID[1] [95% CI], %
6 h	112	8668	19.5% [14.2–25.5%]
12 h	88	6852	14.4% [9.3–20.6%]
24 h	103	8181	17.5% [11.7–24.2%]
48 h	32	2272	18.7% [10.5–27.1%]
72 h	6	387	14.7% [-43.6–7.9%]

[1] Minimal clinically important difference (MCID) in pain intensity is 1/10 (scale between 0 and 10) [2] Intervals considered for the time point: 6 h, 0 to 6 h; 12 h, 7 to 12 h; 24 h, 13 to 24 h; 48 h, 25 to 48 h; and 72 h, 49 to 72 h

at low/unclear risk of bias. Trial sequential analysis is shown in eFigure 24.

Recovery of Gastrointestinal transit

The use of IPLA was associated with lower time to recovery of transit (MD, -3.80 [95% CI, -7.54 to -0.07 h], 8 trials [$n = 454$], low certainty of evidence) (Table 1, eFigure 25). No subgroup analyses were conducted due to the small number of trials.

Hospital length of stay

We found no difference in hospital length of stay (MD, 0.00 [95% CI, -0.03 to 0.03 days], 28 trials [$n = 2,695$], low certainty of evidence) (Table 1, eFigure 27). This finding was consistent across subgroup analyses (eFigure 28).

Persistent postoperative opioid use and incidence of postoperative chronic pain

Postoperative chronic pain and persistent postoperative opioid use were not assessed in any included trial.

Quality of recovery

Functional outcome measurements could not be pooled due to the inconsistency in instrument measures (Return to normal activities, time to mobilization, Surgical Recovery Scale, Quality of Recovery-40) and the limited number of trials ($n = 5$) [54, 63, 66–68]. Following qualitative assessment, results from one trial [54]. suggested a favorable effect from IPLA for postoperative recovery as assessed with the Surgical Recovery Scale 7 days (MD: 7.7 points) and 30 days (MD: 9.3 points) after surgery, while no difference was observed after 45 days (non-significant MD: 6.3 points). One trial observed an improvement in time to mobilization after IPLA (MD: -0.89 h [95% CI:-1.53 to -0.25]) [66]. One trial observed a quicker return to normal activity following IPLA (4.7 to 5.5 days) then control (6.2 days) [67]. However, no improvement was noted with the Quality of Recovery-40 (QoR-40) score (Median of 158 global score after both IPLA and control in one trial [63], MD of -0.8 [95% CI -6.6 to 5.0] after 7 days in one trial [68].

Adverse events

There was no observed effect of IPLA on the incidence of urinary retention (RR, 0.65 [95% CI, 0.07 to 6.33], low certainty of evidence), respiratory depression (no event), vagal reaction/bradycardia (RR, 1.69 [95% CI, 0.24 to 13.08], very low certainty of evidence), anastomotic leak (RR, 1.34 [95% CI, 0.38 to 4.70] very low certainty of evidence), surgical site infection (RR, 0.94 [95% CI, 0.42 to 2.13], low certainty of evidence) or serious adverse events (RR, 2.26 [95% CI, 0.24 to 21.35], low certainty of evidence). We also observed no difference for signs of local anesthetics systemic toxicity (RR, 2.74 [95% CI, 0.30 to 25.40], low certainty of evidence) (eFigures 29–35). Subgroup analyses could not be conducted for adverse events due to the small number of trials. Of note, in one trial, it was reported that local anesthetic nebulization process was a long process and most surgeons believed that laparoscopic visibility was reduced following the nebulization [48]. Only one trial assessed the risk of hospital readmission, [54] and two trials the complication grade (Clavien-Dindo classification) [54, 63]. and there was no statistically significant difference between groups for both outcomes. Trials sequential analyses are shown on eFigures 36–41.

Publication Bias

There was no evidence of potential publication bias based on funnel plot visual assessment and Egger test, except for opioid use at 48 h (p value for Egger test: 0.02) (eFigures 42–49). Publication bias could not be assessed for adverse events and local anesthetic systematic toxicity due to the small number of trials reporting events.

Discussion

We observed a statistically significant reduction in short-term postoperative pain intensity up to 48 h with the perioperative administration of IPLA in the context of intra-abdominal surgery. This finding was also consistent with our modelled risk difference between groups for achieving the MCID. Nevertheless, these results are supported by a low certainty of evidence [34]. IPLA was also associated with a small reduction in opioid use at 24 h, a reduction in postoperative nausea and/or vomiting, and a small reduction in the time for gastrointestinal transit recovery time. We observed no effect of IPLA on hospital length of stay and on the quality of recovery. Although no increase on the incidence of adverse events was observed, important ones, such as respiratory depression, anastomotic leak and anesthetic toxicity, were not frequently assessed, neither was the persistent opioid use and chronic pain.

Our study results are consistent with those of previous systematic reviews showing that IPLA may be beneficial for pain management following intra-abdominal

surgeries [13–15], [69–73]. These reviews were however conducted on specific surgical patient populations, mainly laparoscopic cholecystectomy, which limited the generalizability. Nevertheless, the assessment of whether the observed effect reached a MCID that is relevant for patients was not evaluated in any of these reviews, which is prone to consider any statistical findings as being necessarily clinical important. In addition, assessing the certainty of the evidence, allowing to evaluate if the observed findings are true or are prone to be biased and whether they are likely to be confirmed by future research, is necessary to adequately interpret the summary of effect of meta-analyses. In our work, we assessed both if the summary of effect reached the MCID, and also how confident we could be or not with this observed effect. Such an approach prevents interpreting findings solely on the base of statistical significance when clinical relevance for patients is the most important reason why an intervention is used.

On the other hand, as opposed to previous systematic reviews concluding that the perioperative use of IPLA is safe, frequently based only on the absence of signs of systemic toxicity, [10, 69, 74] we could not reach such a conclusion since we found evidence of potential reporting bias as very few trials ($n = 16$ trials) assessing signs of local anesthetic systemic toxicity. We assessed for other potential plausible adverse effects using a comprehensive approach based on perioperative consensus recommendations for outcomes assessment in perioperative care. We observed a lack of evidence to adequately inform the presence of adverse events associated with IPLA. Our findings were comparable to those of a systematic review conducted in the pediatric population concluding that the intervention was potentially promising but understudied to suggest its use, reemphasizing the lack of trials in this population [75]. While we prioritized dynamic pain over pain at rest in our evaluation, the majority of included trials (66%) did not specify the type of pain intensity scores reported. This limitation has also been highlighted in other perioperative analgesic effectiveness trials and should be considered when interpreting our findings and their clinical relevance [76].

Our systematic review has numerous strengths. We followed a rigorous methodology in line with standardized guidelines for systematic reviews and meta-analyses to assess postoperative analgesic effect [19]. We used an exhaustive and sensible search strategy without language limitation which has been reviewed according to the PRESS guidelines. We also favored patient-reported outcomes at different time points after surgery and we assessed their clinical significance. Finally, we also conducted a trial sequential analysis, which revealed that the actual evidence contributed to information sizes far above the required information sizes for postoperative pain intensity assessment up to 48 h after surgery. Our work also has limitations. First, although we identified several sources of heterogeneity, residual statistical heterogeneity for several outcomes could still not be explained. Second, we conducted multiple subgroup analyses increasing the risk of finding an association that would be incidental. These subgroup analyses should thus be interpreted as exploratory. Third, one third of the trials were judged to be at high risk of bias, suggesting that a significant proportion of the evidence was based on trials of lower methodological quality. Nevertheless, this limitation was accounted for in the certainty of evidence assessment (i.e., downgraded by one level when appropriate), and subgroup analyses showed minimal impact of the risk of bias on the result.

Conclusion

The intraperitoneal administration of local anesthetics may be associated with a small postoperative analgesic effect in an appreciable number of patients undergoing intra-abdominal surgery. Considering the low to very low level of evidence supporting these findings, along with the limited data on adverse effects and long-term outcomes, their adoption as a standard of care intervention cannot be recommended at this stage. There is a need for further randomized controlled trials assessing adverse events, and longer-term outcomes following the perioperative administration of IPLA in this population.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-025-03105-y.

Supplementary Material 1

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Author contributions

Conception and design: M.B, M.V., A.F.T. Acquisition of data: M.B., M.V., S.O., XS., C.M., M.G., H.Z., L.B., F.L.Statistical analysis: M.B., M.V., S.O., X.N., A.F.T. Data interpretation: M.B., M.V., S.O., O.C., A.F.T. Drafting of the manuscript: M.B., M.V., S.O., A.F.T. Revision of the manuscript for important intellectual content: M.B., M.V., S.O., X.S., X.N., C.M., O.C., M.G., H.Z., L.B., F.L., A.F.T. Final approval of the version to be published: M.B., M.V., S.O., X.S., X.N., C.M., O.C., M.G., H.Z., L.B., F.L., A.F.T. Supervision: O.C., A.F.T.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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