Transversus abdominis plane block versus local anesthetic wound infiltration for optimal analgesia after laparoscopic cholecystectomy: A systematic review and meta-analysis with trial sequential analysis

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ABSTRACT

Background: Both transversus abdominis plane (TAP) block and local anesthetic wound infiltration have been used to relieve pain after laparoscopic cholecystectomy. We undertook this systematic review and meta-analysis with trial sequential analysis to determine the best analgesic technique.
Methods: We systematically searched the literature for trials comparing TAP block with wound infiltration after laparoscopic cholecystectomy. The primary outcome was pain score during rest (analogue scale, 0–10) at 2 postoperative hours. Secondary pain-related outcomes included pain scores during rest at 12 and 24 h, pain scores during movement and intravenous morphine consumption at 2, 12 and 24 h, and postoperative nausea and vomiting. Other secondary outcomes sought were block-related complications such as rates of postoperative infection, hematoma, visceral injury and local anesthetic systemic toxicity.
Results: Ten trials including 668 patients were identified. There was a significant difference in pain score during rest at 2 postoperative hours in favour of TAP block when compared with wound infiltration (mean difference [95%CI]: −0.7 [−1.2, −0.2]; I2 = 71%; *p* = 0.008). Pain scores during rest at 12 and 24 h and pain scores during movement at 24 h were also significantly lower with TAP block than wound infiltration. Postoperative morphine consumption and the incidence of postoperative nausea and vomiting were significantly lower in patients who received a TAP block. Data were insufficient to compare block-related complications. The overall quality of evidence was moderate-to-high.
Conclusions: There is moderate-to-high level evidence that the TAP block provides superior analgesia when compared with wound infiltration in patients undergoing laparoscopic cholecystectomy.
Trial registry number: PROSPERO CRD42020208057.

1. Introduction

Laparoscopic cholecystectomy is one of the most frequent abdominal surgeries worldwide [1]. Typically, these procedures are performed on an ambulatory basis or associated with a brief hospital stay. Given the short timeline, strategies to optimize pain control and reduce nausea or vomiting after surgery are therefore key factors to facilitate early hospital discharge. Among the strategies available to address these goals, patients may benefit from the administration of local anesthetic via a transversus abdominal plane (TAP) block, or as infiltration of the trocar sites, also called wound infiltration. While wound infiltration is localized to the incision sites, the TAP block consists of local anesthetic injected in the plane between the internal oblique and the transversus abdominis muscles, intending to anesthetize the sensory nerves supplying the anterior abdominal wall [2].

Several meta-analyses have provided evidence that both TAP block [3] and wound infiltration [4,5] deliver superior pain relief after laparoscopic cholecystectomy when compared to placebo. However, it remains uncertain whether one of these techniques is superior to the other. We therefore undertook a systematic review and meta-analysis with trial sequential analysis to determine whether TAP provides superior analgesia when compared with wound infiltration after laparoscopic

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cholecystectomy.

2. Methods

2.1. Literature search and inclusion criteria

This investigation followed the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) [6] statement recommended process and was prospectively registered on the International Prospective Register of Systematic Reviews (registration number CRD42020208057). The PRISMA flow diagram is depicted in supplementary Fig. 1.

The authors searched the following electronic databases up to June 17, 2020: MEDLINE, Embase, Cochrane Central Register of Controlled Clinical Trials and Web of Science. The following population search terms were applied: Cholecystectomy OR Gallbladder removal. The results of this search were combined with Block OR Transversus abdominis OR TAP OR Local anesthesia OR Wound infiltration OR Trocar site infiltration. The limits of Clinical trials OR Random allocation OR Therapeutic use were then applied to the results. The following words were searched as keywords: Cholecyst*, Gallblader*, Incisi*, Operation*, Operative*, Surger*, Surgical*, Perioperati*, Pain*, Nociception*, Analges*, Anesthe*, Anaesthe*, Transversus abdominis plane block, Transvers*, Infiltration*.

The resulting list of trials generated through this search strategy was limited to randomised controlled trials and human subjects, although no language restrictions were applied to the search. Upon completion of the search, the authors examined the references from all retrieved articles in order to seek applicable trials that the above approach had failed to identify. Finally, an additional search was conducted through Google Scholar™ with any additional relevant trials added to the previous list and authors of clinical trials registered on clinicaltrials.gov but not otherwise identified in the search strategy were contacted directly.

2.2. Population

The meta-analysis addresses adult patients undergoing laparoscopic cholecystectomy.

2.3. Intervention & comparator

Only those trials that investigated pain outcomes and which compared TAP block with wound infiltration were included in this meta-analysis.

2.4. Outcomes

Our pre-defined outcomes were extracted from each article following the routine approach previously described in meta-analyses on acute postoperative pain [7–9]. The pre-determined primary outcome was the pain score during rest at 2 postoperative hours. Given variation in the outcomes observed in the published literature, it was decided to include data in the primary analysis if the resting pain score was reported between 1 and 3 h postoperatively. Secondary pain-related outcomes included: pain scores during rest at 12 and 24 postoperative hours; pain scores during movement at 2, 12, and 24 postoperative hours, cumulative intravenous (iv) morphine consumption at 2, 12, and 24 postoperative hours; and the rate of postoperative nausea or vomiting within the first 24 postoperative hours. Other secondary outcomes sought were those relative to potential block complications including rates of hematoma, postoperative infection, visceral injury and local anesthetic systemic toxicity. We also aimed to capture the resource-related outcome hospital length of stay.

2.5. Trial characteristics

Extracted trial characteristics included the TAP block technique; timing of the TAP block and wound infiltration; concentration and volume of local anesthetic administered; and medications used to manage postoperative analgesia.

2.6. Rating of the studies

The Cochrane Collaboration's Risk of Bias Tool [10] was employed to generate an assessment of methodologic quality for each included trial. Two authors (SG & LA) applied this tool to independently screen, review and score the items for each trial. Disagreements in scoring or extracted data were adjudicated by KRK.

2.7. Data extraction

The texts, tables or images from the source articles were evaluated to extract the number of participants, number of events, means, standard deviations, standard error of means, and 95% confidence intervals (CI). When an article failed to state the sample size or describe their results as a mean and standard deviation or standard error of the mean and 95%CI, we attempted to contact the corresponding author twice by email, with a request for the relevant data or alternately for access to the complete trial dataset. If no reply was received from these requests, we employed the median and interquartile range as approximations of the mean and standard deviation, by estimating the mean as equivalent to the median, and the standard deviation as the interquartile range divided by 1.35 or the range divided by 4 [10]. All opioids were converted to equianalgesic iv morphine doses (iv morphine 10 mg = oral morphine 30 mg = iv tramadol 100 mg = iv pethidine 75 mg = iv fentanyl 100 μg = iv nalbuphine 10 mg = oral hydrocodone 30 mg = oral codeine 165 mg) [11]. For pain scores reported through an 11-point verbal, visual or numeric rating scale, we transposed the results to a 0–10 analogue scale to permit statistical evaluation. Finally, to evaluate the quality of evidence for each of the outcomes reported in this investigation, we applied the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group system [12].

2.8. Statistical analysis

All meta-analyses were conducted using the Review Manager software (RevMan version 5.3.5; Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration 2014). For continuous data, this software estimates the weighted mean differences, and similarly the risk ratio for categorical data between groups, with an overall estimate of the pooled effect. A meta-analysis was conducted when two or more trials reported any given outcome. We calculated the I^2 coefficient as a measure of heterogeneity and with predetermined limits for low (25–49%), moderate (50–74%), and high (> 75%) levels [12]. A random effects model was applied in circumstances when moderate or high heterogeneity was observed; otherwise, a fixed effects model was employed [13]. In an attempt to account for potential sources of heterogeneity, subgroup analyses were conducted for our primary outcome according to the TAP block technique (ultrasound-guided vs laparoscopy-guided), the timing of the TAP block or the wound infiltration (before incision vs after surgery), the prescription of multimodal analgesic treatment (yes or no) and whether the trial was prospectively registered or not prior to inclusion of the first patient. The risk of publication bias associated with the primary outcome was estimated by drawing a funnel plot of the mean difference standard error of rest pain score at 2 postoperative hours (y-axis) as a function of the mean difference of rest pain score at 2 postoperative hours (x-axis) [14] and confirmed with Duval and Tweedie's trim and fill test [15]. This assessment was performed using Comprehensive Meta-analysis Version 2 software (Biostat, Englewood, NJ, USA). Finally, a trial sequential analysis was performed on the

primary outcome to confirm whether firm evidence was reached or not (TSA software version 0.9.5.10 Beta; Copenhagen Trial Unit, Center for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark).

We present results as the mean difference or relative risk (RR) with 95% CI and a 2-sided *p*-value<0.05 was deemed to be significant.

3. Results

Of the 1060 trials identified from the literature search, ten met the inclusion criteria [16–25], representing a total of 668 patients (supplementary Fig. 1). Fig. 1 summarises the risk of bias of the included trials. Three trials were prospectively registered prior to inclusion of the first patient [17,19,22] but discrepancies were noted between the anticipated number and reported number of patients included in two trials [17,22] and one trial was registered retrospectively [21]. We contacted six authors [16–19,21,25], with one providing additional data [18]; means and standard deviations were approximated from median, interquartile range or range in seven trials [17,18,20–24]. Regarding

Fig. 1. Cochrane collaboration risk of bias summary: evaluation of bias risk items for each included study. Green circle, low risk of bias; red circle, high risk of bias; yellow circle, unclear risk of bias. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

our primary outcome, we used the value reported at 3 postoperative hours from two trials [17,19] and at 1 postoperative hour from one trial [25].

Table 1 presents the trial characteristics. The number of included patients per trial ranged from 42 [19] to 132 [16]. All cholecystectomies were performed under general anesthesia and maintained with inhalational agents. All authors reported TAP blocks performed under ultrasound-guidance with the exception of one trial where laparoscopic guidance was used [21]. The TAP block was performed at the beginning of surgery in five studies [17,19–22] and at the end in five studies [16,18,23–25]. Wound infiltration done at the end of surgery under direct vision in all included trials. All authors injected a single bolus of local anesthetic bilaterally, with the exception of two trials in which only a right-sided TAP block was employed [17,25]. Long-acting local anesthetics (bupivacaine 0.25% or 0.5%; levobupivacaine 0.25% or 0.5%, ropivacaine 0.375% or 0.5%) were consistently the local anesthetics reported but a range of volumes were reported (10–25 ml per side for TAP block and 10–40 ml in total for wound infiltration). In six trials, the same type and amount of local anesthetic was given for both the TAP block and wound infiltration [16–18,23–25]; in three trials [19,21,22], the total amount of local anesthetic injected for the TAP block was greater than for the wound infiltration, while in a single study, it was the opposite [20]. No study reported including perineural or intravenous adjuncts. Six authors prescribed multimodal analgesia postoperatively, while four did not [16,19,20,23].

The mean (SD) pain score during rest at 2 postoperative hours was significantly lower for patients who received TAP block compared to those who received LAI, with a mean difference (95%CI) of −0.7 (−1.2, −0.2), $I^2 = 71\%$, $p = 0.008$ (Fig. 2). Subgroup analyses did not reveal any difference in the primary outcome between TAP block techniques (laparoscopic vs ultrasound-guidance; $p = 0.07$), timing of the TAP block or wound infiltration (before vs after surgery; $p = 0.94$), the prescription or not of multimodal analgesic treatment ($p = 0.38$) or whether the trial was prospectively registered or not before inclusion of the first patient ($p = 0.53$). The trial sequential analysis indicated that firm evidence was reached regarding the contribution of TAP block to decrease pain score during rest at 2 postoperative hours (Fig. 3). Regarding the risk of publication bias for the primary outcome, Duval and Tweedie's trim and fill test calculated the combined studies point estimate (95%CI) to be −0.68 (−1.17, −0.18) with a random effects model. Using trim and fill, these values were unchanged, suggesting that no studies are missing.

Based on eight studies [16–18,20–24], the rate of postoperative nausea or vomiting was significantly reduced in the TAP block group from 31% (95%CI: 26%, 37%) to 21% (95%CI: 17%, 26%), with a risk ratio (95%CI) of 0.67 (0.51, 0.88; $I^2 = 0\%$, $p = 0.004$). Table 2 presents the other secondary pain-related outcomes that were all significantly lower in the TAP block group, with the exception of pain scores during movement at 2 and 12 postoperative hours and iv morphine consumption at 2 postoperative hours.

While only two studies reported the rates of block related complications, there were no descriptions of postoperative infection, hematoma or local anesthetic systemic toxicity [18,22]. Only a single trial examined the potential for visceral injury and reported none. [22]. One study reported similar hospital length of stay between groups, without providing figures or additional data [23].

According to the GRADE system, the quality of evidence for the primary outcome was high and moderate-to-high for the secondary outcomes (Table 3).

4. Discussion

This systematic review and meta-analysis explored the analgesic efficacy of TAP block compared to wound infiltration in patients undergoing laparoscopic cholecystectomy. Based on 10 randomised controlled trials, which included a total of 668 patients, we demonstrated that TAP block provides superior postoperative analgesia up to 24 postoperative

Table 1

Trial characteristics. Iv, intravenous; PCA, patient-controlled analgesia.

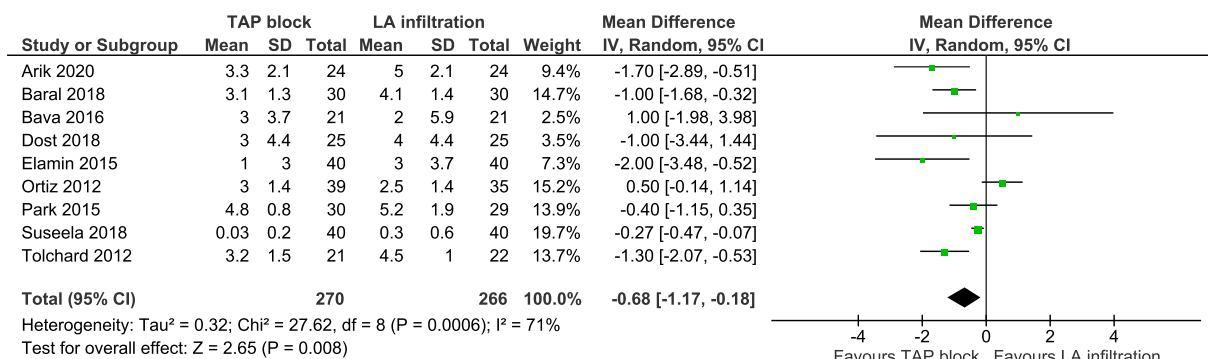| Reference	Group (n)	TAP block technique	Block timing		Local anesthetic injected		Postoperative analgesia
			TAP block	Wound infiltration	TAP block	Surgical infiltration	
Ali et al., 2018 [16]	TAP block (66) Infiltration (66)	Ultrasound-guided, bilateral	End of surgery	End of surgery	Bupivacaine 0.5%, 1 mg. kg^{-1} on each side	Bupivacaine 0.5%, 1 mg. kg^{-1} on each side	iv nalbuphine
Arık et al., 2020 [17]	TAP block (24) Infiltration (24)	Ultrasound-guided, unilateral	Before incision	Before incision	Bupivacaine 0.25%, 20 ml	Bupivacaine 0.25%, 20 ml	iv PCA of tramadol, iv paracetamol, iv dexketoprofen
Baral et al., 2018 [18]	TAP block (30) Infiltration (30)	Ultrasound-guided, bilateral	End of surgery	End of surgery	Bupivacaine 0.25%, 20 ml	Bupivacaine 0.25%, 20 ml	iv paracetamol, iv pethidine
Bava et al., 2016 [19]	TAP block (21) Infiltration (21)	Ultrasound-guided, bilateral	Before incision	Before incision	Ropivacaine 0.375%, 30 ml	Bupivacaine 0.25%, 10 ml	iv PCA of morphine
Dost et al., 2018 [20]	TAP block (25) Infiltration (25)	Ultrasound-guided, bilateral	Before incision	Before incision	Levobupivacaine 0.25%, 30 ml	Levobupivacaine 0.5%, 20 ml	iv PCA of tramadol, iv rescue meperidine
Elamin et al., 2015 [21]	TAP block (40) Infiltration (40)	Laparoscopy-guided, bilateral	Before incision	Before incision	Bupivacaine 0.25%, 50 ml	Bupivacaine 0.5%, 20 ml	Oral paracetamol, oral diclofenac
Ortiz et al., 2012 [22]	TAP block (39) Infiltration (35)	Ultrasound-guided, bilateral	Before incision	Before incision	Ropivacaine 0.5%, 30 ml	Ropivacaine 0.5%, 20 ml	iv ketorolac, oral hydrocodone/ acetaminophen, iv morphine
Park et al., 2015 [23]	TAP block (30) Infiltration (29)	Ultrasound-guided, bilateral	End of surgery	End of surgery	Ropivacaine 0.25%, 40 ml	Ropivacaine 0.25%, 40 ml	iv PCA of morphine, rescue iv tramadol
Suseela et al., 2018 [24]	TAP block (40) Infiltration (40)	Ultrasound-guided, bilateral	End of surgery	End of surgery	Bupivacaine 0.25%, 40 ml	Bupivacaine 0.5%, 20 ml	iv tramadol, iv paracetamol, iv diclofenac
Tolchard et al., 2012 [25]	TAP block (21) Infiltration (22)	Ultrasound-guided, unilateral	End of surgery	End of surgery	Bupivacaine (concentration not specified), 1 mg.kg^{-1}	Bupivacaine (concentration not specified) 1 mg.kg^{-1}	iv fentanyl, iv paracetamol, iv diclofenac, rescue im morphine, rescue oral codeine

Fig. 2. Pain score during rest at 2 postoperative hours in patients undergoing laparoscopic cholecystectomy with TAP block vs wound infiltration.

hours when compared with wound infiltration, with a moderate-to-high level of evidence. More specifically, TAP block reduces pain scores during rest at 2, 12 and 24 postoperative hours, along with iv morphine consumption at 12 and 24 postoperative hours. Of note, the absence of a difference in morphine consumption at 2 postoperative hours may be secondary to a type II error, as only 2 of the included trials reported this outcome.

The mean difference in pain scores during rest is close to 1 at 2 postoperative hours and above 1 at 12 postoperative hours on the 0–10

point analogue scale, a difference which has been shown to be clinically relevant [26]. Indeed, Myles et al. argued from a cohort of 224 patients that any analgesic interventions, which provide a change in pain scores of 10 out of 100 mm on the VAS represent a clinically important improvement and a VAS of 33 or less reflects acceptable pain control [26]. However, it is necessary to balance this improvement against considerations such as the time needed to perform the TAP block, and resulting impact on operating room efficiency [27]. We acknowledge that the TAP block likely requires more time and resources than wound
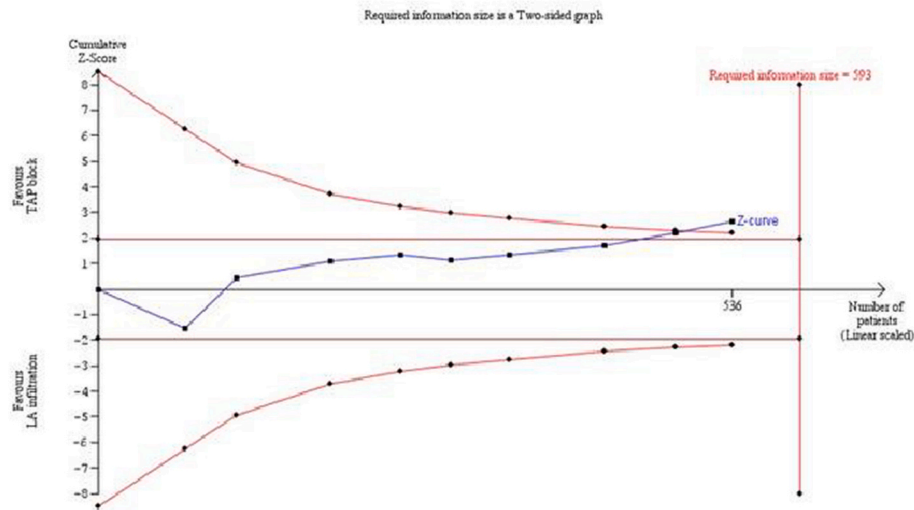
Fig. 3. Trial sequential analysis for pain score during rest at 2 postoperative hours. The cumulative Z curve (blue) crosses the monitoring boundary curve (red), indicating firm evidence that TAP block is superior to no TAP block. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Secondary pain-related outcome. CI, confidence interval; NA, not applicable.

Outcome	Number of trials	References	Total number of patients		Mean difference or Relative risk [95% CI]	I² (%)	p value for overall effect
			TAP block	Wound infiltration			
Pain score during rest at 12 h postoperatively (analogue scale, 0–10)	9	Ali 2018 [16], Arik 2020 [17], Baral 2018 [18], Bava 2016 [19], Dost 2018 [20], Elamin 2015 [21], Ortiz 2012 [22], Suseela 2018 [24]	285	281	−1.3 [−1.9, −0.8]	74	<0.001
Pain score during rest at 24 h postoperatively (analogue scale, 0–10)	8	Arik 2020 [17], Baral 2018 [18], Bava 2016 [19], Dost 2018 [20], Elamin 2015 [21], Ortiz 2012 [22], Park 2015 [23], Suseela 2018 [24]	249	244	−0.6 [−1, −0.3]	73	0.001
Pain score during movement at 2 h postoperatively (analogue scale, 0–10)	6	Arik 2020 [17], Baral 2018 [18], Bava 2016 [19], Dost 2018 [20], Elamin 2015 [21], Park 2015 [23]	170	169	−0.7 [−1.5, 0.2]	53	0.14
Pain score during movement at 12 h postoperatively (analogue scale, 0–10)	5	Arik 2020 [17], Baral 2018 [18], Bava 2016 [19], Dost 2018 [20], Elamin 2015 [21]	140	140	−0.5 [−1.1, 0.1]	44	0.12
Pain score during movement at 24 h postoperatively (analogue scale, 0–10)	6	Arik 2020 [17], Baral 2018 [18], Bava 2016 [19], Dost 2018 [20], Elamin 2015 [21], Park 2015 [23]	170	169	−0.6 [−1, −0.3]	0	<0.001
Intravenous morphine consumption at 2 h postoperatively (mg)	2	Arik 2020 [17], Park 2015 [23]	54	53	−3 [−7.3, 1.3]	75	0.17
Intravenous morphine consumption at 12 h postoperatively (mg)	2	Ali 2018 [16], Arik 2020 [17]	90	90	−6.2 [−12, −0.5]	86	0.03
Intravenous morphine consumption at 24 h postoperatively (mg)	7	Arik 2020 [17], Baral 2018 [18], Bava 2016 [19], Elamin 2015 [21], Ortiz 2012 [22], Park 2015 [23], Suseela 2018 [24]	224	219	−5.3 [−7.8, −2.8]	81	<0.001

infiltration with local anesthetic, particularly when ultrasound-guidance is employed as in the majority of the included trials. Unfortunately, none of the included trials reported the anesthetic- or surgical-related times for comparison in our trial, but previous publications reported an average procedure time in the range of 10 min [2], which might be problematic in the absence of parallel-processing space available for regional anesthetic procedures [27]. Further, the skill of ultrasound guided TAP block represents a technical challenge beyond that of wound infiltration, therefore requiring appropriate training for the performing anesthesiologist. That said, if an ultrasound-guided TAP block cannot be performed, a laparoscopic-guided TAP block may be accomplished by the surgeon, as both approaches have been shown to be equivalent [28].

The technical challenge aside, it is worth noting that the reduction in pain scores observed in our investigation was also associated with a reduction in morphine consumption at 12 and 24 h postoperatively. Even if the magnitude of effect is not particularly impressive, this is of clinical relevance, especially when the concept of rebound pain score might be a concern for some patients [29]. Our results indicate that after the effect of the TAP block wears off, there is no corresponding increase in pain scores at 24 h postoperatively. Of note, and as recently highlighted, rebound pain is not associated with longer-term complications such as persistent post-surgical pain [29].

As a further indicator of impact, our meta-analysis demonstrated a commensurate reduction in the rate of PONV in favour of the TAP block, with an absolute risk reduction of 10 and a number needed to treat of 10. With PONV being a dominant contributor to prolonged length of stay and unplanned hospitalization after ambulatory surgery [30], and given that laparoscopic cholecystectomy is frequently done as an outpatient

Table 3

Quality of evidence assessment for each outcome sought. PONV, postoperative nausea and vomiting; LAST, local anesthetic systemic toxicity.

Quality assessment								Summary of findings
Outcome	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Total number of participants	Conclusion	Quality of evidence (GRADE)
Pain score during rest at 2 postoperative hours (analogue scale, 0–10)	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	536	Reduced pain score in TAP block groups	High quality (⊕ ⊕ ⊕⊕)[e]
Pain score during rest at 12 postoperative hours (analogue scale, 0–10)	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	566	Reduced pain score in TAP block groups	High quality (⊕ ⊕ ⊕⊕)[e]
Pain score during rest at 24 postoperative hours (analogue scale, 0–10)	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	493	Reduced pain score in TAP block groups	High quality (⊕ ⊕ ⊕⊕)
Pain score during movement at 2 postoperative hours (analogue scale, 0–10)	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	339	No difference between groups	High quality (⊕ ⊕ ⊕⊕)[e]
Pain score during movement at 12 postoperative hours (analogue scale, 0–10)	No major limitations[a]	Moderate inconsistency	No serious indirectness[c]	No serious imprecision[d]	No publication bias	280	No difference between groups	High quality (⊕ ⊕ ⊕⊕)[e]
Pain score during movement at 24 postoperative hours (analogue scale, 0–10)	No major limitations[a]	No inconsistency	No serious indirectness[c]	No serious imprecision[d]	No publication bias	339	Reduced pain score in TAP block groups	High quality (⊕ ⊕ ⊕⊕)
iv morphine consumption at 2 postoperative hours	Two studies sought this outcome	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	107	No difference between groups	Moderate quality (⊕ ⊕ ⊕O)[f]
iv morphine consumption at 12 postoperative hours	Two studies sought this outcome	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	180	Reduced consumption in TAP block group	Moderate quality (⊕ ⊕ ⊕O)[f]
iv morphine consumption at 24 postoperative hours	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	443	Reduced consumption in TAP block group	High quality (⊕ ⊕ ⊕⊕)[e]
Rate of PONV within the first 24 postoperative hours	No major limitations[a]	No inconsistency	No serious indirectness[c]	No serious imprecision[d]	No publication bias	583	Less PONV in TAP block group	High quality (⊕ ⊕ ⊕⊕)[e]
Incidence of postoperative infection	Two studies sought this outcome	Not estimable, as no event occurred	No serious indirectness[c]	Not estimable, as no event occurred	No publication bias	134	Not estimable, as no event occurred	Not applicable
Incidence of postoperative hematoma	Two studies sought this outcome	Not estimable, as no event occurred	No serious indirectness[c]	Not estimable, as no event occurred	No publication bias	134	Not estimable, as no event occurred	Not applicable
Incidence of LAST	Two studies sought this outcome	Not estimable, as no event occurred	No serious indirectness[c]	Not estimable, as no event occurred	No publication bias	134	Not estimable, as no event occurred	Not applicable
Hospital length of stay	One study sought this outcome	Not estimable as reported by one study	No serious indirectness[c]	Not estimable, as no figures provided	No publication bias	60	Not estimable, as no figures provided	Not applicable

[a] As all trials has mainly a low risk of bias on the different items, we estimated this does not represent a major limitation.

[b] I^2 above 50% or not applicable, as only one trial reported this outcome.

[c] Consistent definition of the reported outcome.

[d] No serious imprecision as the clinical decision would not be modified whether the upper of lower boundary limit of the confidence interval represented the truth.

[e] Although there was a concern about inconsistency, we did not rate down the quality of evidence because not every criterion appeared to justify rating down by one level. Moreover, there was consistent evidence from randomised controlled trials, with no plausible confounders.

[f] We rated down for limitations, as two trials reported this outcome.

procedure, we believe that our finding suggests tangible benefits for both patient recovery and potentially hospital resource use. Of note, we were unable to capture any directly reported data related to hospital resource outcomes, such as length of stay in post-anesthetic care unit or in hospital, or rate of readmission following PONV after ambulatory surgery. Given regional anesthesia is one pillar of accelerated and enhanced recovery programs [31], offering benefits to both patients and hospitals, we suggest this area as a focus of further research.

We recognize several weaknesses inherent in this meta-analysis. To begin, our hypotheses and subgroup analyses were unable to explain the coefficient of heterogeneity observed in the analysis of our primary outcome. This elevated heterogeneity may be secondary to the subjectivity of the outcome itself; indeed, pain score reports might be influenced by many parameters such as gender and age [32]. There are also surgical reasons that likely contribute to this heterogeneity including the different surgical techniques employed and the experience of the surgeons, neither of which are taken into account in our subgroup analyses. In addition, we were unable to draw any conclusion for a number of our predefined outcomes such as complications after local anesthetic injections, reflecting the absence of data on these outcomes in the majority of included trials. Further, a minority of trials employed a mass of local anesthetic that varied between groups. These differences in doses may potentially favour one intervention group over the other. The impact of this factor is uncertain and likely contributes to the observed

heterogeneity, given that the impact of volume on spread within the TAP plane vs administration into the wound directly makes comparisons between volumes largely arbitrary. Finally, only 3 of the 10 included trials were prospectively registered prior to inclusion of the first patient. The lack of rigor around trial registration, together with the occasional unknown or high risk of bias determined in our assessment of the included trials, warrants acknowledgement that methodologic inconsistencies have an unquantified potential to impact validity of the results.

Despite these potential drawbacks, there is high-to-moderate level evidence that TAP block provides superior analgesia when compared with wound infiltration in patients undergoing laparoscopic cholecystectomy, and reduces postoperative nausea and vomiting during the first 24 postoperative hours.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinane.2021.110450.

Author's contributions

Sina Grape: This author searched the literature, assessed the articles, extracted the data, performed the statistical analysis and wrote the primary manuscript.

Kyle Robert Kirkham: This author analysed the data and contributed to the manuscript.

Liliane Akiki: This author assessed the articles and extracted the data.

Eric Albrecht: This author designed the analysis, searched the literature, assessed the articles, extracted, performed the statistical analysis and contributed to manuscript.

Declaration of Competing Interest

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No conflict of interest declared by the other authors.

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