의학석사 학위논문

Transverse abdominis plane block compared with patient-controlled epidural analgesia following abdominal surgery: a meta-analysis and trial sequential analysis

복부 수술 후 환자 조절 경막외 진통법과 배가로근면 신경차단술 비교 : 메타분석과 임상시험 순차분석

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국문 초록

복부 수술을 한 환자에서 수술 후 통증 조절을 위해 환자 조절 경막외 진통법 (TEA) 과 배가로근면 신경차단술 (TAPB) 이 사용되고 있다. 이 두 방법의 진통 효과 및 부작용을 비교하는 여러 메타분석이 있었지만 연구 수가 적고 연구 간의 이질성으로 인해 결론이 제한적이었다. 본 논문에서는 Medline, EMBASE, Cochrane 중앙 라이브러리 데이터베이스를 사용하여, 2022년 9월까지 출판된 TEA와 TAPB을 비교한 무작위 대조 시험을 대상으로 메타분석을 하였다. 일차 평가 변수는 수술 후 12시간의 휴식 시 통증 점수로 지정하였다. 총 22개의 연구, 1975명의 환자가 포함되었다.

분석 결과 수술 후 12시간의 휴식 시 통증 점수는 TEA 그룹에서 유의하게 낮았다(평균차 0.58, 95% 신뢰 구간 − 0.01, 1.15, P=0.04, I^2=94%). 이외에도 수술 후 48시간의 휴식 시 통증 점수 (평균차 0.59, 95% 신뢰 구간 0.15, 1.03, P=0.009, I^2 = 86%) 및 수술 후 48시간의 운동 시 통증 점수 (평균차 0.53, 95% 신뢰 구간 0.07, 0.99, P = 0.03, I^2=76%) 도 TEA 그룹에서 유의하게 낮게 나타났다. 수술 후 보행 가능까지의 시간은 TAPB 그룹에서 짧았고 (평균차 −4.52, 95% 신뢰구간 −8.68, −0.36 P=0.03), 수술 후 24시간의 저혈압 빈도 (평균차 0.30, 95% 신뢰구간 0.13, 0.71, P=0.006)과 수술 후 72시간의 저혈압 빈도 (평균차 0.17, 95% 신뢰구간 0.06, 0.48, P<0.001)도 TAPB 그룹에서 낮게 나타났다.

수술 후 12시간의 휴식 시 통증 점수에 대해 임상시험 순차분석을 해보았을 때 TEA 그룹에서 통증 점수가 유의하게 낮게 나타났으나 결과 분석에 필요한 표본 크기에 도달하지 못했고, 수술 후 24시간의 휴식 시 통증 점수에 대해서는 통증 점수에 유의한 차이가 없으면서 결과 분석에 필요한 필요한 표본 크기에 도달하지 못한 것을 알 수 있었다.

포함된 연구의 비뚤림 위험성이 높은 점, 결과의 근거 수준이 낮은 점, 포함된 연구 사이의 이질성이 큰 점, 임상시험 순차분석 시 표본 크기가 부족한 것으로 나타난 점 등을 고려해볼 때 본 논문에 제한점이

존재하고, 추가적인 연구가 필요할 것으로 보인다.

주요어 : 수술 후 통증, 개복술, 복강경 수술, 경막외 마취, 신경 차단, 메타 분석
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목 차

표 목차

그림 목차

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1. Introduction

Postoperative pain control has been important for patient satisfaction, lower complication rates, shorter hospital stays, and lower medical costs. In addition, with the recent emergence of the concept of enhanced recovery after surgery, interest in early recovery has grown, and multimodal and active control of pain in surgical patients is becoming increasingly important.

Previously, it was recommended to perform thoracic epidural analgesia (TEA) for analgesia in patients who underwent major abdominal surgery, but TEA has various risks such as catheter failure, hypotension, urinary retention, epidural abscess, and epidural hematoma. Since transversus abdominis plane (TAP) block has been introduced, it is increasingly being used. TAP block is to block the thoracoabdominal nerves by injecting drugs, either with or without the installation of a catheter, under ultrasound-guided or direct visualization.

So far, there have been several meta-analyses comparing TEA and TAP blocks after abdominal surgery [1-3]. Previous meta-analyses showed that there was no significant difference in postoperative pain scores. However, previous meta-analyses found it difficult to draw a definitive conclusion due to the limitations

regarding the small number of studies, the small number of total participants, and the large heterogeneity among studies.

The purpose of our meta-analysis is to provide an updated analysis to compare the analgesic effect, functional outcomes, and side effects of TEA and TAP blocks in patients who underwent open or laparoscopic abdominal surgery under general anesthesia. Accordingly, we collected prospective randomized controlled trials (RCTs) and performed a meta-analysis, systematic review, and trial sequential analysis.

2. Methods

The current systematic review with meta-analysis to compare TAP block with TEA was conducted according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [4] and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements [5]. The protocol was registered on PROSPERO (registration number: CRD42021241020). There were no deviations from the pre-registered protocol. We carried out a systematic search of the Medline, Embase and the Cochrane Central Register of Controlled Clinical Trials from inception to December 18, 2021. The search was updated on September 2022 during the manuscript revision process. The search strategy of Medline was (Epidural anaesthesia OR Epidural anesthesia OR Caudal anaesthesia OR Caudal anesthesia OR Epidural injection OR Epidural drug administration OR Epidural analgesia) AND (Abdominal wall block OR Abdominal wall injection OR Abdominal wall analgesia OR Abdominal wall anesthesia OR Transversus Abdominal wall block OR Transversus abdominis plane block OR Transversalis abdominis block OR Transverse abdominal plane block OR TAP block). We included only randomized controlled trials, which were published in the English

language. RCTs comparing TAP block with TEA in adult patients undergoing open or laparoscopic abdominal surgery under general anesthesia were included. Two authors (YHJ and WHK) independently screened the search results using the title and abstract. The full texts of potentially eligible articles were evaluated for their inclusion. We used only Review Manager (RevMan version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, Oxford, United Kingdom) to select the studies and did not use any other reference manager software.

After determining all included studies, the risk of bias in individual studies was evaluated using the bias domains described in the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0. [6] including the following domains: allocation concealment (selection bias), random sequence generation (selection bias), incomplete outcome data (attrition bias), blinding of participants and personnel (performance bias), selective reporting (reporting bias), and other sources of bias (other bias). Disagreements were resolved by discussion between the two authors or, if needed, by the involvement of another author.

The level of certainty of the evidence for all our study outcomes was determined using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system, which

consists of five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias [7].

Data including inclusion and exclusion criteria, sample size, the technique of TAP block (method of localization, unilateral or bilateral, site of injection, single shot or continuous catheter technique, type of local anesthetics, or TEA (method of localization, type of local anesthetic, bolus and infusion protocol) and postoperative analgesia regimen were collected by one author (YHJ), the accuracy of which was confirmed by another author (WHK).

The primary outcome was the pain score at rest at 12 h postoperatively. The secondary outcomes were the postoperative pain score at rest at 0–2 h, 24 h, 48 h, and 72 h, and the postoperative pain score on movement at 0–2 h, 12 h, 24 h. 48 h, and 72 h. The following outcomes were also included; interval intravenous morphine equivalent consumption at 0–24 h, 24–48 h, 48–72 h; failure rate; incidence of postoperative nausea and vomiting (PONV); incidence of hypotension at 24 h and 72 h.

In general, Visual Analog Scale (VAS) and NRS are considered to be different scales, and it is not appropriate to directly equate the numbers between them. However, we made the assumption of a one–to–one correspondence between the two scales. For example,

they considered NRS 2 points as equivalent to VAS 2.0.

Statistical analysis

We conducted analyses using Review Manager (RevMan version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, Oxford, United Kingdom).

Continuous variables were extracted as mean and standard deviations. If trials reported continuous variables as median and interquartile range, the mean was assumed to be equivalent to the median and the standard deviation was estimated to be the interquartile range divided by 1.35 [4]. We used a random-effects model (inverse variance method for a continuous outcome and Mantel-Haenszel method for a dichotomous outcome) to approximate the effect size of outcome variables. We presented the effect size as a pooled odds ratio (OR), pooled mean difference (MD) with a 95% confidence interval (CI), and depicted a forest plot.

Statistical heterogeneity was assessed by the coefficient I^2. We graded heterogeneity according to predetermined thresholds for high (≥75%), moderate (50-74%), and low (25-49%) levels [8,9]. We assessed publication bias by drawing and visually examining a funnel plot. Duval and Tweedie's trim and fill test and Egger's

linear regression test were also used to evaluate the publication bias using Stata/SE version 13.0 (StataCorp, College Station, TX, USA).

We conducted a trial sequential analysis (TSA) with TSA Viewer (Version 0.9.5.10 Beta, Copenhagen Trial Unit, 2016, Copenhagen, Denmark) [10]. All studies in the three subgroups of open, laparoscopic, and combined surgery were included for each TSA. TSA conducts a cumulative meta-analysis, which depicts a Z curve of the pooled observed effect using the cumulative number of participants and events. TSA constructs two different boundaries for preference for intervention or control group or futility - a conventional boundary for conventional significance ($P < 0.05$) and the trial sequential boundary (O' Brien-Fleming significance boundary). TSA also provides the required information size which means the sufficient sample size required to confirm or reject a certain effect of the study intervention. The required information size was estimated with an 80% power and alpha error of 5%. We depicted two-sided 5% symmetrical O' Brien-Fleming significance boundaries as well as a conventional boundary.

3. Results

A total of 1281 publications were identified according to our search strategy. After screening 1281 titles and abstracts, 192 duplicate studies and 326 irrelevant studies were excluded. Finally, 22 RCTs were included after carefully reviewing the full text. **Figure 1** shows details of the screening and exclusion process.

The baseline characteristics of our included randomized trials are summarized in **Table 1**. Studies were published between 2011 and 2022. A total of 1975 patients participated, of which 997 were in the TAP block group, and 978 of them were in the epidural group. Of the 22 studies [11-32], 3 studies were subjected to the patients who underwent laparoscopic surgery [11,22,32], 15 studies were to open surgery [12-14,16-21,23,24,26,27,30,31] and 4 studies subjected to both types of surgery [15,25,28,29].

The risk of bias assessment is shown in **Figure 2**. Most of the studies were evaluated as at a high risk of performance bias and detection bias, due to not performing adequate blinding of participants, personnel, or the outcome assessor.

Out of the 22 studies, 10 studies [11, 14-16, 20, 24, 26, 27, 29, 30] used NRS to measure pain scores, 11 studies [12, 13, 17-19, 21-23, 25, 31, 32] used VAS and 1 study [28] did not record pain scores. Our primary outcome of

the pain score at rest at 12 h after surgery was significantly different between the TAP block and TEA group favoring TEA group (MD 0.58, 95% CI 0.01, 1.15, P=0.04: **Figure 3**), with significant heterogeneity (I^2=94%, P<0.01). The pain score at rest at 24 h was also not significantly different between the two groups. (MD 0.44, 95% CI −0.18, 1.05, P=0.16; **Figure 4**) with high heterogeneity (I^2=96%, P<0.01).

TSA showed the cumulative observed effect of z−curve for postoperative pain score at rest at 12 h exceeded both the conventional boundary and the O' Brien−Fleming significance boundary and remained outside of both boundaries (**Figure 5**). This means postoperative pain score at rest at 12 h was significantly lower in the TEA group. However, the number of patients did not surpass the required sample size for this outcome.

Meanwhile, the cumulative z−curve of postoperative pain score at rest at 24 h did not cross any of the two boundaries, which means that the pain score at 24 h does not significantly differ between the two groups. However, as the cumulative z−score did not enter the area of futility and the required information size was not achieved (**Figure 6**).

Funnel plot of our primary outcome illustrate some symmetric properties, suggesting the absence of publication bias

(Supplemental Figures S1–S2). However, the trim and fill test ($p<0.001$) and the Egger's test ($p=0.031$) showed the presence of publication bias.

The results of the meta-analyses of our secondary outcomes were summarized in Supplemental Table S1. TEA group reduced the postoperative pain score at rest at 48 h (MD 0.59, 95% CI 0.15, 1.03, P=0.009, I^2=86%) and pain score on movement at 48 h (MD 0.53, 95% CI 0.07, 0.99, P=0.03, I^2=76%). Interval intravenous morphine equivalent consumption at each time band (0–24 h, 24–48 h, 48–72 h) was similar between the two groups. Functional outcomes of the time to first flatus and hospital length of stay did not significantly differ between groups. However, time to ambulation (MD −4.52 h, 95% CI −8.68, −0.36, P=0.03, I^2=70%) was significantly shorter in the TAP block group compared to the TEA group. Regarding complication rates, the failure rate of the procedure was not significantly different between groups. There was no significant difference in the rate of PONV between groups (OR=0.81, 95% CI 0.39, 1.65, P=0.55, I^2=50%). However, the incidences of hypotension at 24 h and 72 h were significantly higher in the TEA group.

The quality of evidence evaluated with the GRADE system was reported for all primary and secondary outcomes in Supplemental

Table S2.

4. Discussions

In this meta-analysis, we sought to compare the clinical effect and safety of TEA and TAP block as postoperative analgesia in abdominal surgery under general anesthesia. Meta-analysis and TSA were performed based on the 22 prospective RCTs. Our pooled analysis showed that most of the pain scores were not significantly different between groups. The pain scores at rest at 12 h and pain scores at 48 h showed statistical significance. However, the absolute differences were not clinically significant as the differences of less than 1 point on the NRS or VAS are considered clinically insignificant [33, 34]. TSA showed the required sample sizes for the pain scores at rest at 12 and 24 h were not achieved, suggesting that further RCTs are required for confirm conclusion. However, time to ambulation and the incidence of hypotension at 24 h and 72 h were significantly different favoring the TAP block group. Our results should be interpreted carefully given the insufficient information size demonstrated by TSA, high risk of bias of the individual studies, significant heterogeneity, and low or very low quality of evidence for most of our outcomes.

According to the results of our meta-analysis, we found statistically significant difference between TEA and TAP block in

the postoperative pain score at rest at 12 h. And we could not find any significant difference between the two groups in postoperative pain scores at rest and on movement at 24 h. Out of 16 RCTs included in the 24 h pain score analysis, there was significant heterogeneity in the procedural techniques. TAP block was performed as a single injection in 7 RCTs and continuous block in 9 RCTs, while TEA was performed as a continuous block in all cases. As TAP block with a single injection is considered to be effective approximately 10 to 12 hours after administration [35, 36], it was expected that the pain scores at 24 h would be lower in the TAP block group. But our meta-analysis showed no significant difference in the pain score at 24 h. Additionally, subgroup analysis showed no significant difference between TAP block with single injection group and TEA group. This could be due to the the utilization of a multimodal analgesia protocol.

Additionally, we performed TSA to better control type-1 and type-2 errors. According to the adjusted threshold for statistical significance in TSA, TEA showed a lower score than TAP block in postoperative pain scores at rest at 12 h but not at 24 h. However, for both outcomes, the cumulative numbers of participants did not reach the required information size. Given the results of clinically or statistically insignificant results of our meta-analysis for

postoperative pain scores and significant heterogeneity, we can not simply accept the results of TSA for the pain score at 12 h. We think that both TEA and TAP block are effective to control the pain scores and the results of TSA suggest that no conclusion could be drawn until sufficient information size was obtained.

Our meta-analysis of pain scores at other time points showed that there is a significant difference for both pain scores at rest and on movement at 48 h. However, the differences were only 0.59 and 0.53 units on a 10-point scale for the pain score at rest and on movement, respectively. We think that these small differences in pain scores are not clinically meaningful.

Interval intravenous morphine equivalent consumption did not show any significant difference between the TEA group and the TAP block group for 0-24 h, 24-48 h, and 48-72 h. However, we could obtain important results regarding the functional outcomes. The time to the first ambulation was significantly shorter in the TAP block group. Early ambulation is one of the important principles of early recovery after surgery, and previous studies have shown that early ambulation lowers the complication rate and reduces the patient's length of hospital stay [37]. The incidences of hypotension at 24 h and at 72 h were also lower in the TAP block group compared to the TEA group. The occurrence of hypotension

also affects on ambulation. In patients who have undergone high-risk abdominal surgery, orthostatic hypotension, which is commonly observed in those who have received TEA, poses a hindrance to their ability to engage in ambulation [38, 39].

Among the included studies in our meta-analysis, there were no study documenting procedure-related complications such as epidural hematoma. Only the failure rate was reported with no significant difference between groups. However, in general, TAP block is regarded as a simple and safe technique. Among the reported complications are enlarged liver laceration, transient femoral nerve palsy, and bowel hematoma [40], but the incidence can be further reduced by performing it under real-time ultrasound guidance. On the other hand, TEA requires caution because it has a higher risk of complications and may cause major complications such as epidural hemorrhage/hematoma, infection, and epidural abscess [41].

We found significant heterogeneity regarding the surgery type of our included trials. A total of 12 RCTs were analyzed in our meta-analysis for the postoperative pain score at rest at 12 h, with 9 studies on open surgery, 2 studies on laparoscopic surgery, and 1 study on both open and laparoscopic surgery. Among the 16 studies analyzed for the postoperative pain score at rest at 24 h, 12 studies

were on open surgery, 3 studies on laparoscopic surgery, and 1 study on both open and laparoscopic surgery. As laparoscopic surgeries are increasing and the intensity of postoperative pain could differ between open and laparoscopic surgery, more studies comparing the efficacy of TEA and TAP block in laparoscopic surgery are needed.

There have been previous meta-analyses regarding this issue [2,3,42]. In the most recent meta-analysis, Desai et al. [3] reported a significant difference in the pain score at rest at 12 h with 11 RCTs favoring TEA, which was consistent with our analysis. For the pain score at rest at 24 h, there was no significant difference [3]. TSA showed the same results favoring TEA for pain score at rest at 12 h. Hamid et al. [42] published a meta-analysis with six RCTs only for colorectal surgery and reported that TAP block is equivalent to TEA regarding postoperative pain scores but provided better functional recovery with a lower incidence of complications. Our study also demonstrated that the time to ambulation was significantly shorter and the incidences of hypotension at 24 h and 72 h were significantly lower in TAP block group compared to TEA group. Baeriswyl et al. [2] analyzed 10 RCTs for both children and adults. There was no significant difference in their primary outcome of the pain score at rest at 24 h and they concluded that both

techniques are equally effective for both children and adults. TAP block was associated with a fewer incidence of hypotension and reduced length of hospital stay.

Our meta-analysis has several limitations. Firstly, the risk of bias from individual studies is high. The quality of evidence for most of our study outcome is low or very low. There was a high risk of performance bias and detection bias. Most studies did not have detailed descriptions of how they blinded participants, study personnel, and outcome assessor. Secondly, there is significant heterogeneity regarding the research methods of individual studies and the results of the meta-analysis for our study outcomes. The heterogeneous methods of TEA and TAP block administration, injection drugs, drug dose, catheter placement, and postoperative analgesia protocol after surgery make it difficult to pool the study results. Thirdly, for the comparison of hospital length of stay, the criteria for hospital discharge may vary in different institutions, which makes it difficult to compare TEA with TAP block groups. Also for the comparison of the incidence of hypotension, the different diagnostic criteria of hypotension undermine the validity of our results. Finally, we used estimated means and standard deviations from medians and interquartile ranges divided by 1.35. This method is valid only when the distribution of the outcome

variable is similar to the normal distribution. As data on pain score is frequently skewed, our estimation may lead to wrong estimation.

In conclusion, we could not find any significant or clinically meaningful difference in the postoperative pain scores until 72 h after surgery. Regarding pain scores, our meta-analysis may indicate that both techniques are equally effective. Our analysis demonstrated that time to ambulation was significantly shorter and the incidence of hypotension was significantly lower in the TAP block group compared to the TEA group. Regarding these outcomes, TAP block may be a better choice than TEA. However, TSA showed that the required information size has not yet been reached. Given the significant heterogeneity of our meta-analysis, high risk of bias of individual studies and low or very low quality of evidence for most of our outcomes, firm conclusions cannot be drawn but it is not likely that the addition of further studies could prove any clinically meaningful difference in the pain score between these two techniques.

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Abstract

Transverse abdominis plane block compared with patient-controlled epidural analgesia following abdominal surgery: a meta-analysis and trial sequential analysis

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Thoracic epidural analgesia (TEA) and transversus abdominis plane (TAP) block are used for pain control after abdominal surgery. Although there have been several meta-analyses comparing these two techniques, the conclusion was limited by a small number of studies and heterogeneity among studies. Our meta-analysis used the Medline, EMBASE, and Cochrane central library databases from their inception through September 2022. Randomized controlled trials comparing TEA and TAP block were included. The pre-specified primary outcome was the pain score at rest at 12 h postoperatively. Twenty-two RCTs involving 1975 patients were included. Pooled analyses showed the pain score at rest at 12 h postoperatively was significantly different between groups favoring

TEA group (Mean difference [MD] 0.58, 95% confidence interval CI 0.01, 1.15, P=0.04, I^2 = 94%). TEA group significantly reduced the pain score at 48 h at rest (MD 0.59, 95% CI 0.15, 1.03, P=0.009, I^2=86%) and at 48 h at movement (MD 0.53, 95% CI 0.07, 0.99, P = 0.03, I^2=76%). However, there was no significant difference at other time points. Time to ambulation was shorter in TAP block but the incidences of hypotension at 24 h and 72 h were significantly lower in TAP block compared to TEA. Trial sequential analysis (TSA) showed that the required information size has not yet been reached. Our meta-analysis demonstrated there was no significant or clinically meaningful difference in the postoperative pain scores between TEA and TAP block groups. Given the insufficient information size revealed by TSA, the high risk of bias of our included studies, and the significant heterogeneity of our meta-analysis results, our results should be interpreted carefully but it is not likely that the addition of further studies could prove any clinically meaningful difference in pain score between these two techniques.

Keywords : postoperative pain, laparotomy, laparoscopy, epidural analgesia, nerve block, meta analysis
Student Number : 2020-23242

Table 1. Characteristic of the included trials.

Trial	Group-TAP block	Group-Epidural	Surgery	TAP block technique	Local anesthetic for TAP block	Local anesthetic for epidural	Postoperative analgesia
Aditianingsih et 2018 [11]	25	25	Laparoscopic donor nephrectomy with a Pfannenstiel incision	USG, bilateral lateral and unilateral subcostal approach, single-shot injection	0.25% bupivacaine 20 ml for each injection	Single bolus of 0.125% bupivacaine 3ml and continuous infusion of 0.125% bupivacaine at a rate of 6 ml/h	IV morphine PCA
Calixto-Flores 2020 [12]	15	15	Open donor nephroureterectomy	Surgical placement under direct vision, unilateral lateral approach, continuous block	0.375% ropivacaine 15ml bolus injection and continuous infusion of 0.2% ropivacaine at a rate of 2 ml/h	Single bolus of 0.375% ropivacaine 10ml and continuous infusion of 0.2% ropivacaine at a rate of 2 ml/h	Not described
Canakci 2018 [13]	42	42	Cesarean section	USG, bilateral lateral approach, single shot injection	0.25% bupivacaine 20 ml for each injection	Single bolus of 0.5% isobaric bupivacaine 16 ml, morphine 3 ml, and fentanyl 50 mcg (20 ml in total)	Intravenous dexketoprofen
Cata 2021 [14]	35	33	Cytoreductive surgery with hyperthermic intraperitoneal	USG, bilateral lateral and subcostal	Bupivacaine 150mg and liposomal bupivacaine 266mg divided into four quadrants	bupivacaine 0.075% ± hydromorphone 2–5 mcg/mL or	Regular paracetamol, oral nonopioid analgesics (ex.

			chemotherapy	approach, single shot injection		bupivacaine 0.075% ± fentanyl 5 mcg/mL, basal rate 8 mL/h, bolus 3 mL every 10 min	Celecoxib) PRN
Felling 2018 [15]	92	87	Open, laparoscopic and robotic abdominal surgery	USG, bilateral lateral approach, single-shot injection	133 mg liposomal bupivacaine 20 ml on each side	Continuous infusion of 0.0625% bupivacaine and fentanyl of unspecified concentration at rate of 6-8 ml/h	Regular paracetamol, naproxen and gabapentin
Ganapathy 2015 [16]	26	24	Laparotomy	USG, bilateral lateral and subcostal approach, continuous block	1. Lateral TAP: 10 ml ropivacaine 0.5% bolus injection on each side 2. Subcostal TAP: 20 ml ropivacaine 0.5% bolus injection on each side 3. Single lateral and subcostal TAP injections followed by a combined continuous infusion of ropivacaine 0.35% at a rate of 4-5 ml/h on each side for 72 h	0.25% bupivacaine 5 ml ± additional 0.25% bupivacaine 3 ml boluses followed by a continuous postoperative infusion of 0.1% bupivacaine and hydromorphone 10 mcg/ml at a rate of 8 ml/h for 72 h	Regular paracetamol, naproxen and gabapentin
Hughes 2015 [17]	49	44	Open liver surgery	Surgical placement under direct vision, unilateral	40 ml levobupivacaine 0.125% bolus injection in total followed by a combined continuous injection of	10 ml levobupivacaine of unspecified concentration followed by a	IV morphine PCA

				lateral and rectus sheath approaches, continuous block	levobupivacaine 0.375% at a rate of 4 ml/h for 48 h	continuous infusion of 0.1% levobupivacaine at an unspecified rate	
Kandi 2015 [18]	30	30	Laparotomy	USG, bilateral lateral approach, single-shot injection	20 ml bupivacaine 0.125% on each side	Continuous infusion of 0.125% bupivacaine at a rate of 4-8 ml/h for 48 h unless still needed for pain relief	Paracetamol and morphine PRN
Lyer 2017 [19]	33	36	Open lower abdominal surgery	USG, bilateral lateral approach, just above the iliac crest, single-shot injection and subsequent top-ups at 8 hourly intervals for 48 h	20 ml 0.125% bupivacaine on each side for the first bolus and subsequent top-ups of the same volume and concentration at 8 hourly intervals for 48 h	First dose at the end of surgery – 0.125% bupivacaine 10 ml and subsequent top-ups of the same volume and concentrations at 8 hourly intervals for 48 h	Regular paracetamol and IV tramadol
Mathew 2019 [20]	20	20	Total abdominal hysterectomy with a Pfannenstiel incision	Landmark-guided bilateral lateral approach, single-shot injection	15 ml bupivacaine 0.25% on each side	1. Intraoperative: 2% lidocaine 6-8 ml with epinephrine 5 mcg/ml every 90 min 2. Postoperative: 0.125%	Morphine PRN

						bupivacaine 8 ml every 6 h for 24 h	
Niraj 2011 [21]	27	31	Laparotomy	USG, bilateral subcostal approach, continuous block	1 mg/kg bupivacaine 0.375% boluses every 8 h through each catheter for 72 h	0.25% bupivacaine 20 ml followed by a continuous postoperative infusion of 0.125% bupivacaine and fentanyl 2 mcg/ml at a rate of 6-12 ml/h and a bolus of 2 ml with a lockout period of 30 min for 72 h	Regular paracetamol and IV tramadol, epidural analgesia if TAP block failed and IV morphine PCA if epidural failed
Niraj 2014 [22]	30	31	Laparoscopic abdominal surgery	USG, bilateral lateral approach, continuous block and bilateral subcostal approach, single-shot injection	0.375% levobupivacaine 2.5 ml/kg in total for all four quadrant blocks followed by a continuous infusion of 0.25% levobupivacaine through both catheters at a rate of 8-10 ml/h for 48 h	0.25% bupivacaine 20 ml followed by a continuous infusion of 0.125% bupivacaine and fentanyl 2 mcg/ml at a rate of 8-12 ml/h and a bolus of 2 ml with a lockout period of 30 min	Regular paracetamol and diclofenac with tramadol PRN
Raghvendra 2016 [23]	30	30	Total abdominal hysterectomy	USG, bilateral lateral approach, single-shot injection	0.75% ropivacaine 1.5 ml/kg at a maximum dose of 150 mg on each side	0.5% ropivacaine 10-15 ml ± additional 0.5% ropivacaine 5 ml bolus to reach a sensory block up to T8 followed by a continuous postoperative	IV tramadol PCA

						infusion of 0.2% ropivacaine at a rate of 10 ml/h	
Rao Kadam 2013 [24]	22	19	Laparotomy	USG, bilateral lateral or subcostal approach depending on the surgery, continuous block	0.375% ropivacaine 20 ml bolus injection each side followed by a continuous infusion of	0.2% ropivacaine 8-15 ml followed by a continuous postoperative infusion of 0.2% ropivacaine at a rate of 5-15 ml/h for 72 h	Regular paracetamol and IV fentanyl PCA
Regmi 2019 [25]	35	35	Lower abdominal surgery	USG, bilateral lateral approach, continuous block	0.25% bupivacaine 0.4 ml/kg at a maximum dose of 2 mg/kg on each side followed by a continuous infusion of 0.125% bupivacaine at a rate of 5 ml/h through each catheter for 24 h	0.25% bupivacaine 15 ml followed by a continuous postoperative infusion of 0.125% bupivacaine at a rate of 5-12 ml/h for 24 h	IV morphine PCA
Revie 2012 [26]	49	44	Open liver surgery	Surgical placement under direct vision, unilateral lateral and rectus sheath approaches, continuous block	0.25% levobupivacaine 20 ml bolus injection	Continuous infusion of 0.1% bupivacaine and fentanyl 2 mcg/ml at a rate of 7-10 ml/h	Regular paracetamol for all patients and unspecified opiate PCA in TAP group
Shaker 2018 [27]	32	35	Laparotomy	USG, bilateral lateral and subcostal	Liposomal bupivacaine 10 ml and 0.5% bupivacaine on each side	0.125% bupivacaine and fentanyl 2 mcg/ml at an unspecified	Paracetamol, ketorolac, gabapentin and opioid PRN

						rate	
Torgeson 2018 [28]	41	37	Laparoscopic or open colorectal surgery	USG, bilateral, subcostal approach, single-shot injection	Liposomal bupivacaine 40 ml (133 mg) on each side	Boluses of bupivacaine 0.0625% and fentanyl 2 mcg/ml intraoperatively followed by continuous postoperative infusion at a rate of 6 ml/h and a bolus of 2 ml with a lock out period of 30 min for 48 h	Regular paracetamol and ketorolac
Turan 2022 [29]	260	254	open or laparoscopic-assisted abdominal surgery, including colorectal procedures and hysterectomies	USG, bilateral lateral and subcostal	0.25% bupivacaine 10ml and liposomal bupivacaine 5ml (266 mg) on each side	Bolus of bupivacaine 0.1% and patient-controlled boluses allowed per hospital policy (usually 3 ml each, every 15 min)	IV hydromorphone or fentanyl, IV PCA
Wahba 2014 [30]	22	22	Laparotomy	USG, bilateral subcostal approach, continuous block	0.25% bupivacaine 20 ml on each side followed by boluses of 0.25% bupivacaine 15 ml every 8 h through each catheter	0.125% bupivacaine 10 ml followed by a continuous postoperative infusion of 0.125% bupivacaine at a rate of 6-8 ml/h	IV morphine PCA
Wu 2013 [31]	27	29	Laparotomy	USG, bilateral subcostal	0.375% ropivacaine 20 ml on each side	Before anesthesia induction: 0.25% ropivacaine 8 ml	IV morphine PCA

				approach, single-shot injection		Intraoperative: Continuous infusion of ropivacaine	
Xu 2020 [32]	55	55	Laparoscopic colorectal cancer surgery	USG, bilateral lateral and subcostal approach, continuous block	0.375% levobupivacaine 2.5 ml/kg in total for all four quadrant blocks followed by a continuous infusion of 0.25% levobupivacaine through both catheters at a rate of 8 ml/h for 48 h	Before anesthesia induction: 0.25% ropivacaine 6-8 ml at least 20 min Intraoperative: 0.25% ropivacaine 5ml/h Postoperative: 0.15% ropivacaine and 0.5 μg/ml sufentanil at a continuous infusion rate of 4 ml/h, 3ml bolus on patient request and 15 min lock-out time, for 48 h.	Regular flurbiprofen, sufentanil PRN

Abbreviations: TAP transverse abdominis plane, *USG* ultrasound guided, *IV* intravenous, *PCA* patient-controlled analgesia, *PRN* pro re nata

Figure 1. PRISMA (Preferred Reporting times for Systematic Reviews and Meta-analyses) 2020 flow diagram.

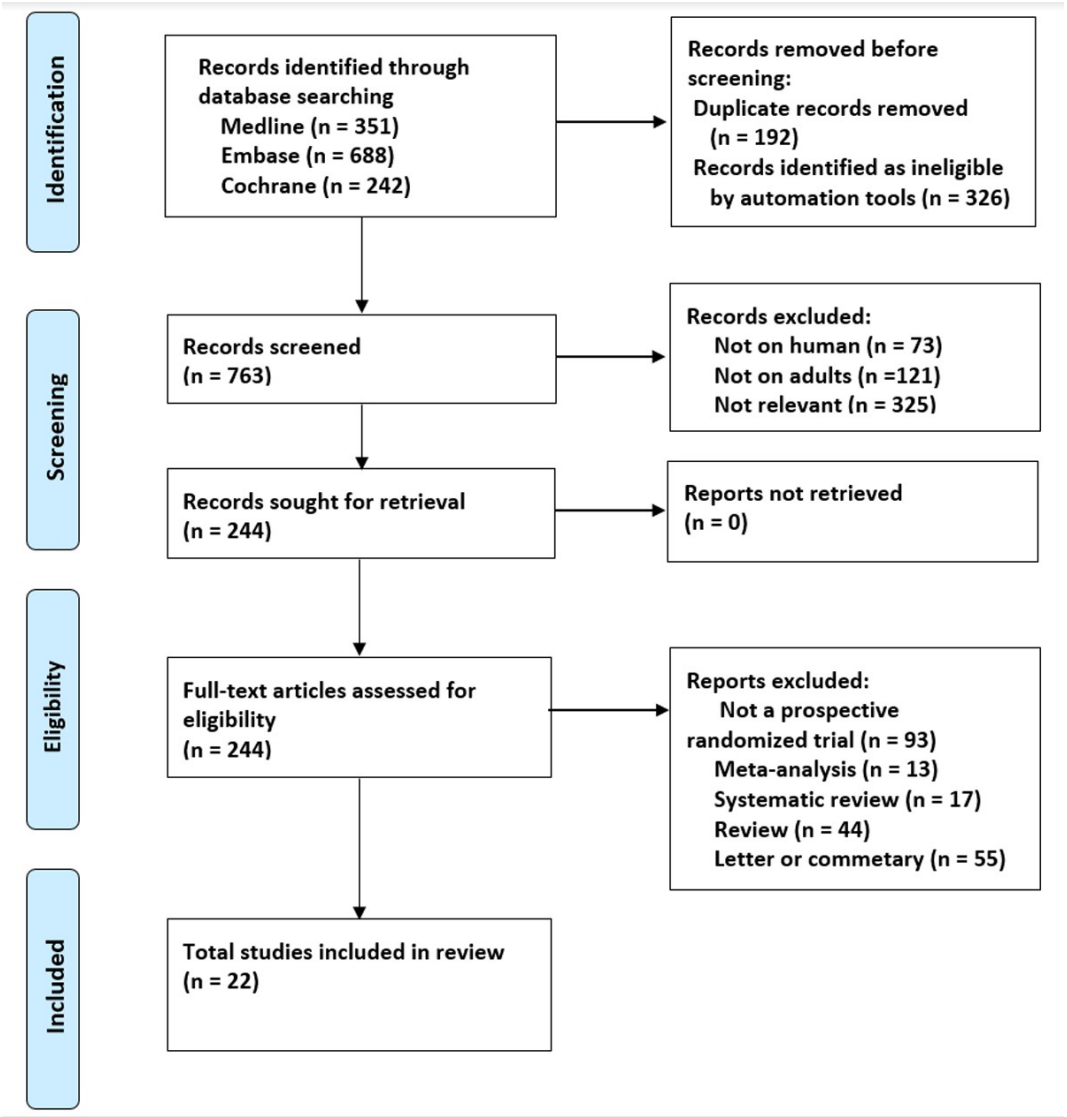


Figure 1. Summary of risk of bias assessment.

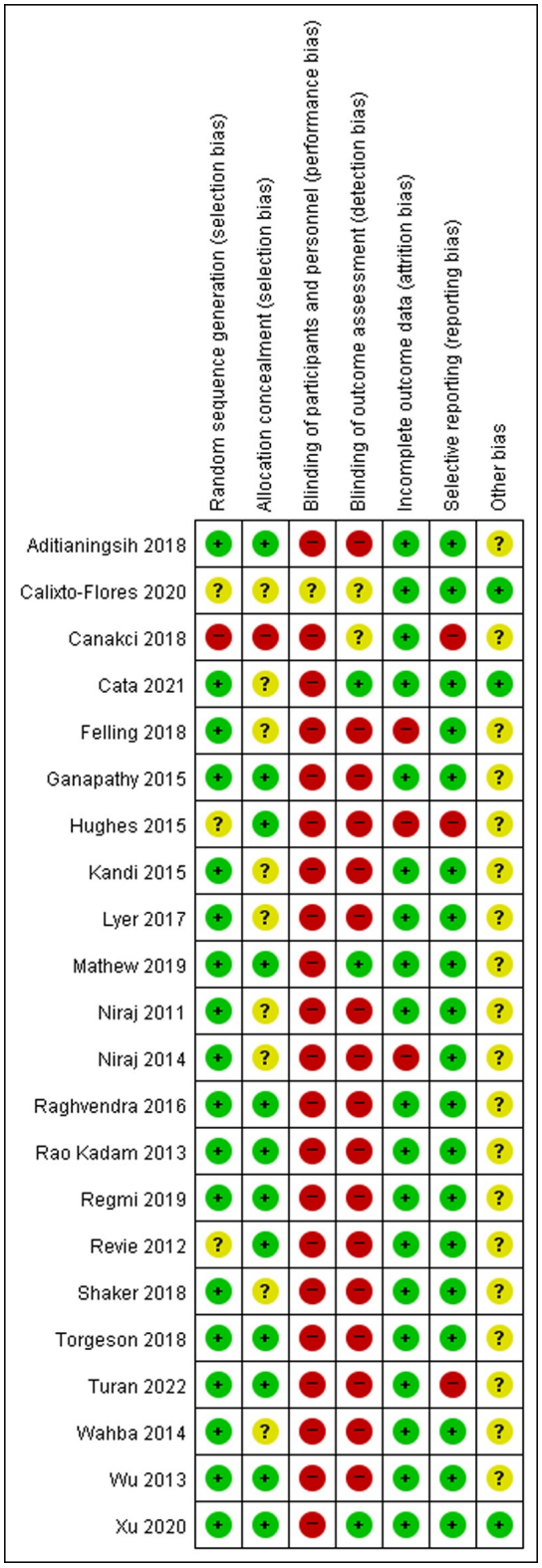


Figure 3. Forest plot of comparison: Pain score at rest at 12 h after surgery.

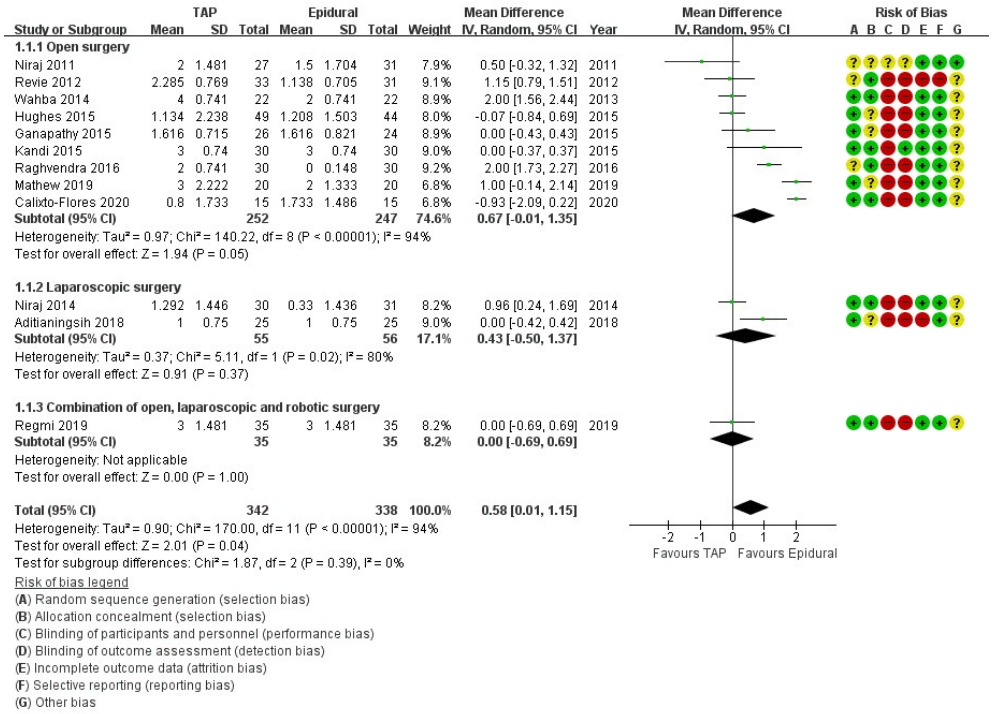


Figure 4. Forest plot of comparison: Pain score at rest at 24 h after surgery.

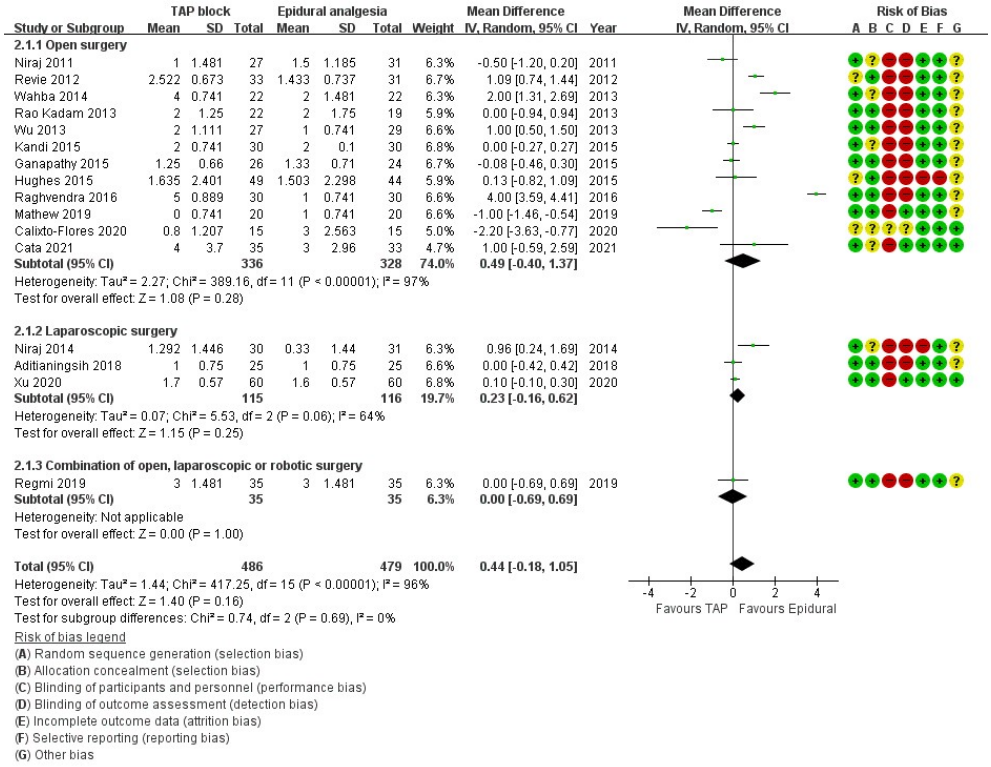


Figure 5. Trial sequential analysis for the pain score at rest at 12 h.

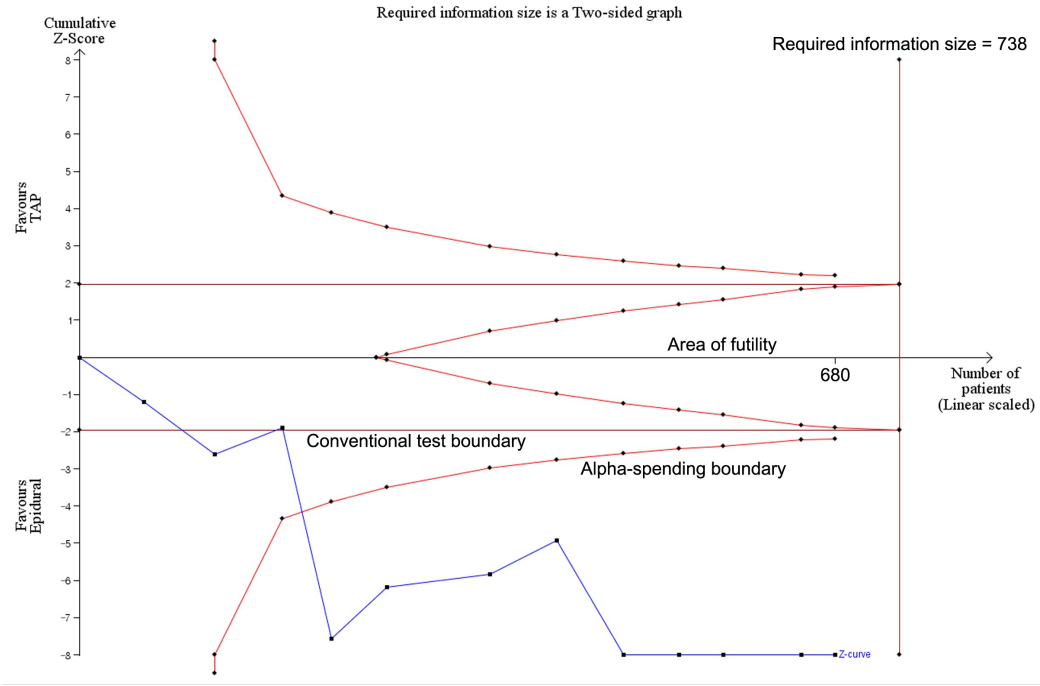
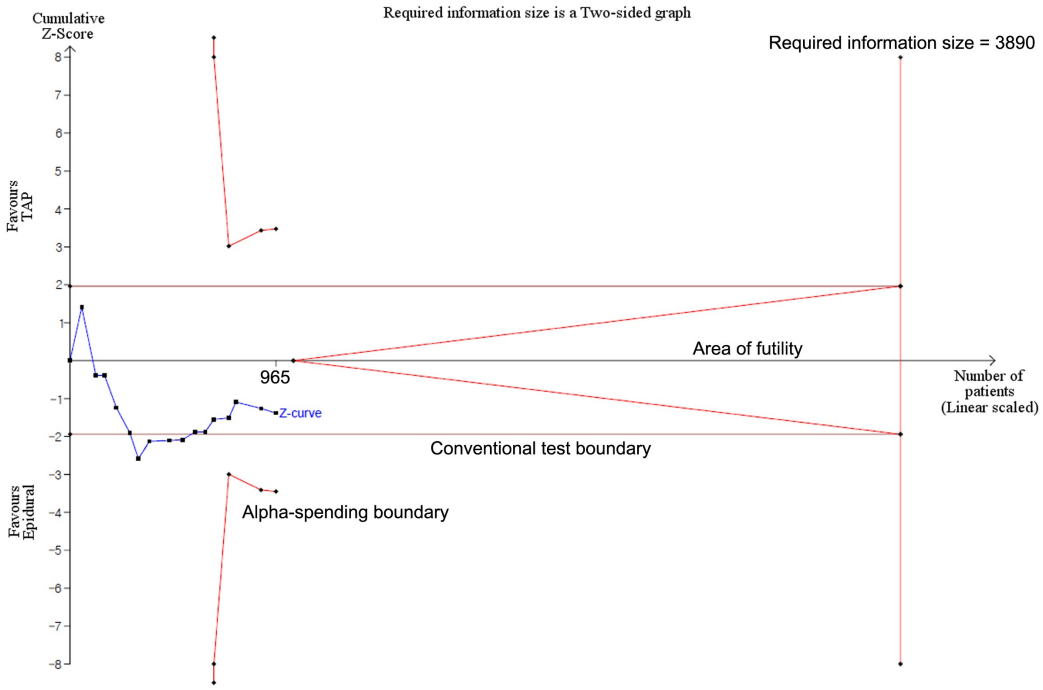
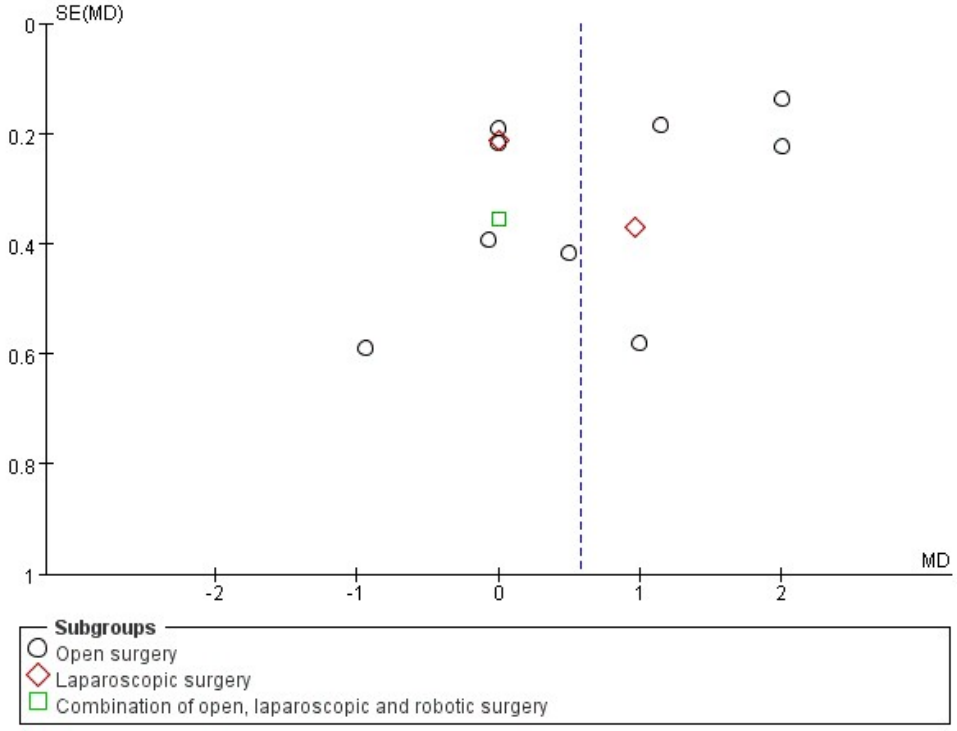


Figure 6. Trial sequential analysis for the pain score at rest at 24 h.

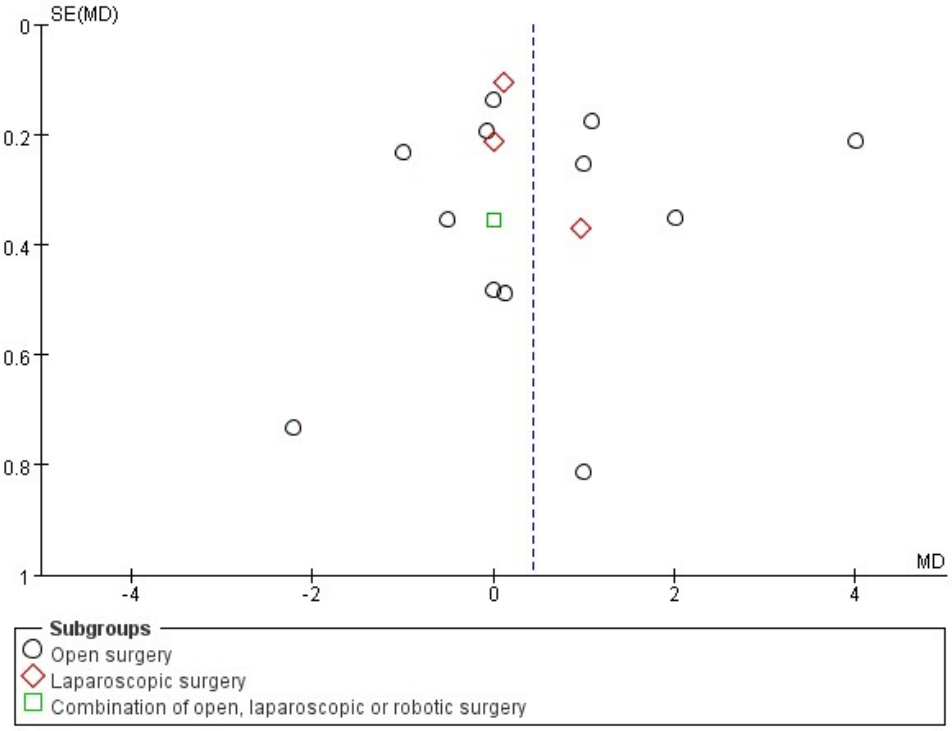


Supplemental Figure S1. Funnel plot of comparison: Pain score at rest at 12 h.

On the y-axis standard error of the mean difference of the outcome of interest (measure of trial size) was plotted as a function, on the x-aixs, of the mean difference of the outcome.



Supplemental Figure S2. Funnel plot of comparison: Pain score at rest at 24 h.



Supplemental Table S1. Results of the meta-analysis of the secondary outcomes.

Outcomes	Number of studies included	TAP group	Epidural group	Effect size (95% CI)	I^2 (%)	P-value*
Pain score at rest						
at 0 – 2 h [11,14,17,18,20,22-26,30-32]	13	413	404	0.46 (-0.17 to 1.08)	94	0.15
at 48 h [14,16,17,21,22,24,26,27,30-32]	11	358	351	0.59 (0.15 to 1.03)	86	0.009
at 72 h [16,17,21,24,29,31]	6	406	401	0.07 (-0.09 to 0.24)	0	0.38
Pain score on movement						
at 0 – 2 h [11,14,17,22-26,30-32]	11	308	299	0.79 (-0.10 to 1.68)	93	0.08
at 12 h [11,16,17,21-23,25,26,30]	9	277	273	0.70 (-0.08 to 1.47)	91	0.08
at 24 h [11,14,16,17,21-26,30-32]	13	416	409	0.86 (-0.42 to 2.13)	98	0.19
at 48 h [14,17,21,22,24,26,30-32]	9	300	295	0.53 (0.07 to 0.99)	76	0.03
at 72 h [16,17,21,24,31]	5	151	147	-0.12 (-0.73 to 0.49)	58	0.70
Interval intravenous morphine equivalent consumption						
at 0 – 24 h [11,14-17,20,23-25,27,30,31]	12	415	403	3.01 (-3.55 to 9.58)	96	0.37
24 – 48 h [14-17,24,27,30]	7	278	264	-15.62 (-34.70 to 3.46)	98	0.11
48 – 72 h [14-17,24,27,30]	7	278	264	-1.05 (-5.33 to 3.24)	85	0.63

Postoperative clinical course						
Time to first flatus (hours) [15-17,22,28,30-32]	8	342	329	2.45 (-0.59 to 5.49)	86	0.11
Time to ambulation (hours) [11,17,22,30,32]	5	181	177	-4.52 (-8.68 to -0.36)	70	0.03
Hospital length of stay (days) [14,15,18,22,24,26,28,32]	8	338	323	-0.37 (-0.89 to 0.15)	79	0.16
Complication rate						
Procedure failure rate [11-19,21-26,28,31,32]	18	656	640	0.91 (0.48 to 1.72)	0	0.76
Incidence of nausea and vomiting [18,20,28,31,32]	5	173	171	0.81 (0.39 to 1.65)	50	0.55
Incidence of hypotension at 24 h [14,25,27]	3	102	103	0.30 (0.13 to 0.71)	0	0.006
Incidence of hypotension at 72 h [16,17,31]	3	102	97	0.17 (0.06 to 0.48)	0	<0.001

The data are presented as mean difference or risk ratio with its 95% confidence interval (CI).

TAP = transversus abdominis plane

P-value is the result of the test for overall effect.

Supplemental Table S2. Quality of the evidence (GRADE approach).

	No. of studies	No. of TAP group	No. of Epidural group	Quality assessment					Quality of evidence
				Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	
Pain score at rest									
at 0-2h after surgery	13	413	404	Serious [a]	Serious [b]	Not serious	Not serious	Likely [e]	⊕⊖⊖⊖ very low
at 12 h after surgery	12	342	338	Serious [a]	Moderate [c]	Not serious	Not serious	Likely [e]	⊕⊕⊖⊖ Low
at 24 h after surgery	15	486	479	Serious [a]	Serious [b]	Not serious	Serious [d]	Likely [e]	⊕⊖⊖⊖ very low
at 48 h after surgery	11	358	351	Serious [a]	Moderate [c]	Not serious	Not serious	Likely [e]	⊕⊕⊖⊖ Low
at 72 h after surgery	6	406	401	Serious [a]	Not serious	Not serious	Not serious	Likely [e]	⊕⊕⊖⊖ Low
Pain score on movement									
at 0-2h after surgery	11	308	299	Serious [a]	Moderate [c]	Not serious	Not serious	Likely [e]	⊕⊕⊖⊖ low
at 12 h after surgery	10	277	273	Serious [a]	Serious [b]	Not serious	Not serious	Unlikely	⊕⊕⊖⊖ Low
at 24 h after surgery	13	416	409	Serious [a]	Serious [b]	Not serious	Not serious	Likely [e]	⊕⊖⊖⊖ very low

at 48 h after surgery	9	300	295	Serious [a]	Serious [b]	Not serious	Not serious	Unlikely	⨁⨁⨀⨀ Low
at 72 h after surgery	5	151	147	Serious [a]	Moderate [c]	Not serious	Not serious	Unlikely	⨁⨁⨁⨀ Moderate
Interval intravenous morphine equivalent consumption									
at 0 – 24 h	12	415	403	Serious [a]	Serious [b]	Not serious	Not serious	Unlikely	⨁⨁⨀⨀ Low
24 – 48 h	7	278	264	Serious [a]	Serious [b]	Not serious	Not serious	Unlikely	⨁⨁⨀⨀ Low
48 – 72 h	7	278	264	Serious [a]	Serious [b]	Not serious	Serious [d]	Likely [e]	⨁⨀⨀⨀ very low
Postoperative clinical course									
Time to first flatus (hours)	8	342	329	Serious [a]	Serious [b]	Not serious	Not serious	Unlikely	⨁⨁⨀⨀ Low
Time to ambulation (hours)	5	181	177	Serious [a]	Moderate [c]	Not serious	Not serious	Unlikely	⨁⨁⨁⨀ Moderate
Hospital length of stay (days)	8	338	323	Serious [a]	Not serious	Not serious	Not serious	Unlikely	⨁⨁⨁⨀ Moderate
Complication rate									
Procedure failure rate	18	656	640	Serious [a]	Not serious	Not serious	Not serious	Unlikely	⨁⨁⨁⨀ Moderate
Incidence of nausea and vomiting	5	173	171	Serious [a]	Not serious	Not serious	Serious [d]	Likely [e]	⨁⨁⨀⨀ Low

Incidence of hypotension at 24 h	3	102	103	Serious [a]	Not serious	Not serious	Not serious	Too few studies	⊕⊕⊖⊖ Low
Incidence of hypotension at 72 h	3	102	97	Serious [a]	Not serious	Not serious	Not serious	Too few studies	⊕⊕⊖⊖ Low

The basis for the assumed risk is provided in footnotes.

[a] In most studies, blinding was not performed for participants, personnel and outcome assessors. Final decision to rate down quality of evidence by one level for risk of bias.

[b] I^2 was above 50% with wide variance of point estimates across studies. Final decision to rate down quality of evidence by one level for serious inconsistency.

[c] Even though the I^2 was above 50%, the point estimates did not vary widely between studies. Final decision to not rate down quality of evidence for moderate inconsistency.

[d] Confidence interval included null effect as well as appreciable benefit and/or harm. Final decision to rate down quality of evidence by

one level for serious imprecision.

[e] Final decision to rate down quality of evidence by one level for serious publication bias.

High quality means that we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality means that we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality means that our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low quality means that we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.