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Title: Continuous peripheral nerve blocks (CPNBs) compared to thoracic epidurals or multimodal analgesia for midline laparotomy: a systematic review and meta-analysis

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Running title: Peripheral Nerve Blocks for Midline Laparotomy

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Continuous peripheral nerve blocks (CPNBs) compared to thoracic epidurals or multimodal analgesia for midline laparotomy: a systematic review and meta-analysis

Running title: Peripheral Nerve Blocks for Midline Laparotomy
Abstract

Background:
Continuous peripheral nerve blocks (CPNBs) have been investigated to control pain for abdominal surgery via midline laparotomy while avoiding the adverse events of opioid or epidural analgesia. The review compiles the evidence comparing CPNBs to multimodal and epidural analgesia.

Methods:
We conducted a systematic review using broad search terms in Medline, EMBASE, Cochrane. Primary outcomes were pain scores and cumulative opioid consumption at 48 hours. Secondary outcomes were length of stay and postoperative nausea and vomiting (PONV). We rated the quality of the evidence using Cochrane and GRADE recommendations. The results were synthesized by meta-analysis using Revman.

Results:
Our final selection included 26 studies (1,646 patients). There was no statistically significant difference in pain control comparing CPNBs to either multimodal or epidural analgesia (low quality evidence). Less opioids were consumed when receiving epidural analgesia than CPNBs (mean difference (MD) -16.13 [95% CI -32.36, -0.10], low quality evidence) and less when receiving CPNBs than multimodal analgesia (MD -31.52 [95% CI -42.81, -20.22], low quality evidence). The length of hospital stay was shorter when receiving epidural analgesia than CPNBs (MD -0.78 days [95% CI -1.29, -0.27], low quality evidence) and shorter when receiving CPNBs than multimodal analgesia (MD -1.41 days [95% CI -2.45, -0.36], low quality evidence). There was no statistically significant difference in PONV comparing CPNBs to multimodal (high quality evidence) or epidural analgesia (moderate quality evidence).
Conclusion:

CPNBs should be considered a viable alternative to epidural analgesia when contraindications to epidural placement exist for patients undergoing midline laparotomies.

Keywords: Laparotomy; Regional Anesthesia; Nerve Block; Catheter; Systematic Review; Abdominal Surgery; Multimodal analgesia
Glossary of terms

- AAA = aortic abdominal aneurysm
- BMI = body mass index
- Bupi = Bupivacaine
- CI = confidence interval
- CPNBs = Continuous peripheral nerve blocks
- ERAS = Enhanced Recovering After Surgery
- HPB = hepatobiliary
- IV = inverse variance
- LAST = local anesthetic systemic toxicity
- LB = liposomal bupivacaine
- Levobupi = Levobupivacaine
- LOS = length of stay
- MD = mean difference
- n/a = Not applicable
- NR = Not reported
- NRS = numerical rating scale
- OME = oral morphine equivalents
- OR = odds ratio
- PCA = patient controlled analgesia
- PONV = postoperative nausea and vomiting
- PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses
• QUIPS = QUality In Prognosis Studies
• RCT = randomized controlled trial
• Ropi = Ropivacaine
• RSB = rectus sheath block
• SD = Standard deviation
• TAP = transversus abdominus plane
• UGI = Upper gastrointestinal
• VAS = visual analogue scale
Introduction

It is estimated that 43.8% of the North American population will undergo abdominal surgery during their lifetime. [1] These procedures are associated with high rates of complications, particularly for comorbid or older patients. [2] Many physiologic insults are associated with inadequate pain control. [3] Given that pain increases postoperative morbidity, recovery time, duration of opioid use, health care costs, and quality of life impairment, optimizing pain control can help to mitigate the negative consequences of surgery. [3]

Open laparotomies, particularly those in the upper abdomen, are associated with respiratory complications if pain is not adequately controlled. [4] The incidence of postoperative pulmonary complications can be as high as 39% in high risk abdominal surgery, with increasing incidence each day that patients are not mobilized. [5] Currently, intravenous opioids are the most common medication for postoperative pain control following surgery. [6] Intravenous opioids attenuate the pain response and associated complications; however, in high doses some complications are exacerbated including respiratory depression, pneumonia, and ileus, which in turn contribute to longer hospital stays and higher health care costs. [7]

The most common regional anesthetic technique used for abdominal surgery is thoracic epidural. [8] Studies have consistently found that patients using thoracic epidural analgesia experience superior pain control and quality of life after laparotomy. [9] Guidelines for “Management of Postoperative Pain” and “Enhanced Recovering After Surgery (ERAS) for Gastrointestinal Surgery” both strongly recommend thoracic epidural analgesia. [10,11] There remains reservation regarding the use of
epidurals due to potentially devastating complications, such as epidural hematoma and abscesses. [12] In an attempt to avoid complications from systemic opioids or epidural placement, peripheral nerve blocks have been investigated. Initial reports described single shot nerve blocks, which were effective at reducing pain; however, much of the reduction in opioid consumption occurs within the first 24 hours. [13] Additionally, these studies do not compare the techniques to each other, thus their relative efficacy and risk remain unclear.

Previous reviews have compared single shot transversus abdominus plane (TAP) blocks to placebo and wound infiltration. [14] Another review compared paravertebral blocks to epidural catheters, with only 4 of 20 using continuous catheters. [15] One systematic review examined the analgesic efficacy of wound infiltration compared to epidural analgesia. [16] The review included multiple types of incisions increasing the clinical heterogeneity. The purpose of this review is to determine the relative analgesic efficacy of continuous peripheral nerve blocks (CPNBs) compared to (i) multimodal analgesia and (ii) epidural analgesia for patients undergoing abdominal surgery via a midline laparotomy.
Methods

Search strategy

Our protocol was registered on PROSPERO (2017:CRD42017051770) at the beginning of the review process. Using broad search terms, we conducted a comprehensive search in three databases: Ovid Medline, EMBASE, and the Cochrane Library. Our search strategy was developed in consultation with an expert medical librarian. We adapted the search terms used in Ovid Medline (Supplemental Table 1) for other databases. We initially completed the search November 30, 2016 later repeating it on July 1, 2018.

We did not apply language restrictions to this search. We conducted a search of the grey literature using OpenSIGLE (Supplemental Table 2) and conference abstracts. Once studies were selected for inclusion, a reference search and a forward citation search (using Web of Science) were conducted for each included study.

Inclusion criteria

Population

We included randomized controlled trials and cohort studies involving adult patients (aged >18 years) undergoing elective abdominal surgery via a midline laparotomy. Urology, general surgery, or vascular surgery procedures performed through an open midline laparotomy were included.
Intervention

We included studies using regional anesthesia techniques to block pain transmission from the peripheral nerves of the abdominal wall. To be included, the technique must have blocked pain transmission on a continuous basis either by continuous infusion of a local anesthetic agent via a catheter for \( \geq 48 \) hours, intermittent bolus injection of local anesthetic for \( \geq 48 \) hours or by administering liposomal bupivacaine. We included studies that compared these techniques to either 1) Continuous epidural analgesia covering the abdominal dermatomes and/or 2) multimodal analgesia with systemic opioids.

Outcomes

The primary outcomes of interest were pain control as measured by visual analogue scale (VAS) or numerical rating scale (NRS) and opioid consumption at 48 hours. All VAS pain scores reported on a scale from 0-100mm were converted to NRS pain scores by dividing by 10. Opioid consumption was compared by converting the reported consumption into oral morphine equivalents (OME). [17] To be included studies must have reported either pain scores or opioid consumption up to 48 hours postoperatively. Secondary outcomes of interest were length of stay in hospital and postoperative nausea and vomiting (PONV).

Exclusion criteria

Studies were excluded if they involved obstetrical, gynecologic, or trauma surgery. Studies involving children (<18 yo) or animals were also excluded. Case studies, case series, and reviews were excluded. If >20% of patients were treated on an urgent or emergent basis the study was excluded. Likewise,
studies involving >20% laparoscopic procedures were excluded. Patients undergoing procedures via other incisions were excluded.

Selection procedure
Two investigators (JB, CM) independently reviewed title, abstract and full text to assess inclusion and exclusion criteria. If consensus could not be reached between the two investigators, then a third investigator (RC, KK) resolved the disagreement.

Risk-of-bias assessment
We critically appraised each cohort study that met the inclusion criteria for potential biases using a modified version of the QUality In Prognosis Studies (QUIPS) tool for cohort studies. [18] Each randomized controlled trial (RCT) was assessed using the Cochrane Risk of Bias Tool. [19] Two of four investigators (JB, CM, RC, JK) independently rated each domain in every study. [19] We categorized a study as having a high risk of bias in a domain if the bias was likely to change the results significantly. [19]

Once all the studies were assessed independently, the reviewers came to a consensus on each domain. If a consensus was not reached, a third reviewer resolved the disagreement. Funnel plots were created for the primary outcomes to assess for publication bias if more than 10 studies reported a particular outcome. The overall certainty of the evidence was rated using the Cochrane handbook and GRADEpro software (Evidence Prime, Inc., McMaster University, Ontario, Canada). [19]
Data extraction

One of four reviewers (JB, CM, RC, JK) extracted pertinent data points from each included study using a standardized data extraction form. Each data point was then checked for accuracy by a second reviewer (JB, CM, RC, JK). If further information or clarification was required, we contacted the corresponding author of the study.

Statistical analysis

We synthesized the data using random-effects meta-analysis with Revman 5.3.5 software (The Nordic Cochrane Centre, Copenhagen, Hovedstaden, Denmark). We analyzed continuous data using inverse-variance mean differences and dichotomous data using Mantel–Haenszel odds ratios. Statistical heterogeneity was assessed using an I^2 statistic. Forest plots are displayed and interpreted using mean difference (MD) rather than standardized mean difference since pain scores were all converted to NRS and all opioid consumption was converted to OME in keeping with Cochrane recommendations. [19] Any study with 3 comparison groups, the overall means of the shared control group with half the number of patients were used for comparison as per the Cochrane recommendations. [19] Since this review included various CPNBs, forest plots include subgroup analyses for each CPNB separately. These subgroup analyses were planned to evaluate the relative contribution of each technique toward the combined effect, and to evaluate the efficacy of each CPNB separately.

Our PROSPERO registration included two planned sensitivity analyses. First, any studies found to have a high risk of bias in one or more categories would be removed. Since 19 of our 26 studies had at least one high risk of bias category, we modified our sensitivity analysis to remove studies with two or
more high risk categories. A sensitivity analysis was performed to examine the effect of upper versus lower midline laparotomy (i.e. above or below the umbilicus) on the primary outcomes. In addition to the planned sensitivity analyses, we conducted additional posthoc sensitivity analyses. We separated the results of those studies using an epidural solution which included opioids. We performed a sensitivity analysis removing cohort studies from the meta-analyses.

Results

Our search strategy yielded 19,889 results. Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [20], we generated a flow chart of our selection process (Figure 1). We contacted 31 authors for additional information. Of these authors, 9 responded with the specific data we requested. [21-29] One author [30] responded by providing us with the raw anonymized study data. Two authors responded but did not have the data requested. One author declined to provide additional information unless given authorship on this review. Two authors had emails that were not current, and we were unable to reach them.

After title/abstract screening, correspondence with authors, hand-searching and full-text assessment for eligibility, 26 studies involving 1,646 patients met the final inclusion for this review. Two studies [31,32] were cohort studies while the rest for RCTs. Two studies [33,34] were able to be divided into 2 subgroups for a total of 28 comparisons.
Risk of Bias

We found that 19 studies had high potential for bias in one domain and, of those, 9 had high potential for bias in at least two domains. The most common source of bias was blinding of participants and personnel. Blinding of personnel was considered to be high risk of bias if the study protocol allowed to differential treatment. Random sequence generation was considered to be high risk of bias if the described technique was known to not adequately randomize, whereas studies were rated as moderate or unclear risk of bias if the technique was not adequately described in the paper. Blinding of outcome assessment was deemed high risk of bias if the assessors were aware of the assignment to a study group.

Funnel plots did not suggest publication bias for pain scores or opioid consumption comparing between CPNB and multimodal analgesia (Supplemental Figure 1). The funnel plots were not created for the comparisons between CPNB and epidural analgesia since there were less than 10 studies.

Multimodal analgesia

The types of multimodal analgesia were not specified a priori in our protocol. Two studies did not describe their multimodal analgesia approach. [35,36] The following agents were used as part of the multimodal analgesia strategy in included studies: Acetaminophen/Paracetamol (20 studies), non-specific NSAIDs (12 studies), COX-2 inhibitors (4 studies), gabapentin (3 studies), and tramadol (3 studies). In two studies, both the intervention and control groups were given patient controlled epidural analgesia. [25,37] These studies were considered multimodal in this review the intervention group also received epidurals, lessening the potential effect of the CPNB.
Wound Catheter

Three studies evaluated the effectiveness of wound catheters on pain management following midline laparotomies. [28,34,38] All three studies compared the use of wound catheters to systemic opioids, while Zheng et al. also compared wound catheters to epidurals. See table 1 for baseline characteristics, local anesthetic dosing, comparison groups. The wound catheters were all placed by surgeons.

Zheng et al. found no difference in pain scores at rest or with movement between groups. Although Zheng et al. displayed these results as figures, exact numbers were not available for meta-analysis. [34] Overall, patients with wound catheters used less opioids over 48 hours (mean difference (MD) -21.46mg [95% confidence interval (CI) -40.33, -2.59], P=0.03, I²=94%, 3 studies, n=403) (Figure 2).

Wang et al. reported higher rates of PONV among wound catheter participants compared to controls. [28] Zheng et al. recorded lower PONV and sedation scores in the wound catheter group compared to the patient controlled analgesia (PCA) group, particularly in the first 12 post-operative hours. There was a shorter length of stay among participants in the wound catheter group than participants in the PCA group. Rates of PONV and length of stay were not significantly different between the wound catheter and epidural groups. [34]

Intraperitoneal Catheters

The evidence for intraperitoneal catheters comes from two double-blind placebo-controlled RCTs using the ON-Q system. [37,39] In the first RCT, Baig et al studied 66 patients undergoing elective
colectomy, and found that intraperitoneal catheters decreased the 48-hour opioid consumption. There was no significant difference in pain scores except for postoperative day two afternoon. The generalizability of the study is limited by the lack of multimodal analgesia. [39]

The second RCT consists of 60 patients undergoing colectomy, with both groups also receiving thoracic epidurals. [37] This study also found that an intraperitoneal catheter infusion for three days further decreased the pain scores with movement and coughing at multiple time points within the first week postoperatively. However, this data needs to be interpreted in the context of overall low pain scores (maximum 4/10) in both groups. We were not able to obtain opioid consumption data from the study authors for meta-analysis.

Preperitoneal Catheters

There were 12 studies included involving preperitoneal catheters with seven compared against multimodal analgesia [25,30,31,35,40-42] and 5 compared against epidural catheters [21,24,43-45]. In all cases the catheters were placed by the surgeon during wound closure. In one case, both the preperitoneal and the comparison groups received thoracic epidurals. [25] We considered this study to be comparing against multimodal analgesia with systemic opioids since both groups received epidurals, which we assumed would decrease the overall effect of preperitoneal catheters.

Of the studies comparing preperitoneal catheters to multimodal analgesia, only four out of seven reported 48-hour pain scores. There was no significant difference in pain at 48 hours, either individually or pooled (MD -0.01 [95% CI -0.12, 0.10], p=0.84, I^2=0%, 4 studies, 294 patients). The
pooled results of 6 studies showed less cumulative opioid consumption at 48 hours in patients with preperitoneal catheter than those receiving multimodal analgesia (Figure 2). When compared to epidurals, there was no significant difference in pain scores (MD 0.38 [95% CI -0.10, 0.86], p=0.12, I²=12%, 3 studies, 114 patients). The pooled results of these two studies showed less opioid consumption among patients with epidurals (Figure 3).

Compared to placebo, preperitoneal catheters reduced length of stay in 2 out of 4 studies reporting hospital stay duration; however, the overall effect was not statistically significant (MD -1.77 days [95% CI -5.04, 1.49], p=0.29, I²=98%, 3 studies, 192 patients) (Supplemental Figure 2). [25,35,40,42] Epidurals reduced length of stay compared to preperitoneal catheters in 2 of 3 studies (MD 1.11 days [95% CI 0.71, 1.51], p<0.001, I²=65%, 3 studies, 157 patients) (Supplemental Figure 3). [43-45]

Transversus Abdominus Plane (TAP) Catheters

Five studies involving TAP catheters were included, with two comparing to multimodal analgesia [23,32] and three comparing to epidural analgesia [26,36,46]. In one study the TAP catheters were placed by the surgeon [32], whereas in the other four studies TAP catheters were placed by anesthesiologists under ultrasound guidance  [23,26,36,46]. The opioid groups did not have catheters placed and all patients in those studies received patient control analgesia (PCA) pumps.

Kadam et al. (2011) found a significant reduction in pain scores during coughing in the first two days for patients with TAP catheters compared to multimodal analgesia. [23] Wahba et al found that the epidural group had significantly lower pain scores at all time points compared to the TAP group. [36]
The other three studies found no differences in pain scores. There was no significant difference overall in pain scores compared to multimodal analgesia (MD -1.32 [95% CI -2.70, 0.06], p=0.06, I²=52%, 2 studies, 120 patients) or epidural analgesia (MD 0.89 [95% CI -1.10, 2.88], p=0.38, I²=95%, 3 studies, 133 patients). Both studies comparing to opioid analgesia found a significant reduction in opioid use over 48 hours when patients received TAP catheters (Figure 2). [23,32] The evidence for comparing TAP catheters to epidurals was conflicting. One study comparing TAP to epidural catheters found no difference in opioid consumption [46], one other found a significant reduction in opioid use with epidural analgesia [36], and the last found less opioid use in the TAP group [26] (Figure 3). It must be noted that the study finding more opioid use in the epidural group included a converted dose of the epidural opioids in the total opioid consumption. [26] Both Kadam et al. (2013) and Wahba et al. did not use opioids in their epidural solution. [36,46]

Rectus Sheath Catheters

Two studies involving rectus sheath block (RSB) catheters were included with one comparing to multimodal analgesia [33] and one comparing to epidural analgesia [29]. Purdy et al. had three groups: RSB with intermittent dosing, RSB with continuous infusion, and control (opioid analgesia). [33] The catheters were placed by the surgeon in the Purdy 2018 study and under ultrasound guidance by an anesthesiologist in the Yassin 2017 study.

Purdy 2018 found no differences in 48-hour pain scores between the three groups. The means and standard deviations were not available for meta-analysis. The intermittent dosing group had lower pain at rest at 12 hours; all other time points were not significantly different. [33] Similarly, Yassin 2017
found no differences in pain scores at any time point. [29] In terms of opioid consumption at 48 hours, Purdy 2018 found a reduction among both RSB groups compared to multimodal analgesia (Figure 2), whereas Yassin 2017 found opioid consumption to be significantly lower in the epidural group compared to the RSB group (Figure 3).

**Paravertebral Catheters**

There have been two randomized trials on paravertebral catheters that met inclusion criteria. [22,27] Hutchins et al. studied 48 patients undergoing open pancreatic surgery randomized to T8 paravertebral catheters or T7-8 epidurals. This trial found that while the opioid consumption was decreased within the first 24 hours in the epidural group, there was no difference in opioid consumption at other time points (Figure 3). Moreover, there was no significant difference in pain scores. [22]

In a pragmatic randomized trial of 70 patients comparing bilateral paravertebral versus epidurals, all inserted between T7 to T9, Sondekoppam found that paravertebral catheters provided non-inferior analgesia for the primary outcome of 24-hour pain score with movement. Within the follow-up period of 72 hours, there was no significant difference in pain scores or opioid consumption. Length of stay in hospital was also similar (MD -1.40 days [95% CI -4.31, 1.51], p=0.34, I²=23%, 2 studies, 116 patients) (Supplemental Figure 3). [27]
Overall comparison and sensitivity analyses

Primary outcomes

When comparing the combined effects of all CPNB studies, there was no statistically significant
difference in pain scores between CPNB and either multimodal analgesia or epidural analgesia (MD -
0.35 [95% CI -0.77, 0.07], p=0.10, $I^2=95\%$, 10 studies, 909 patients; MD 0.45 [95% CI -0.13, 1.04],
p=0.13, $I^2=84\%$, 8 studies, 375 patients, respectively)(Table 2 & 3). Patients receiving CPNB used
significantly less opioids than those receiving multimodal analgesia (MD -31.52 [95% CI -42.81, -
-20.22], p<0.001, $I^2=93\%$, 13 studies, 970 patients). This was observed for the subgroups receiving
continuous wound, and preperitoneal catheters (Figure 2). There was not a statistically significant
difference in opioid use between CPNB and epidural analgesia in the overall comparison (MD 16.13
[95% CI -0.10, 32.36], p=0.05, $I^2=94\%$, 8 studies, 342 patients); however, opioid consumption was
reduced for patients receiving epidural analgesia in the preperitoneal, rectus sheath and paravertebral
subgroups (Figure 3).

Secondary outcomes

Length of hospital stay was significantly shorter for the epidural group compared to the CPNB group
(MD 0.78 days [95% CI 0.27, 1.29], p=0.003, $I^2=59\%$, 8 studies, 399 patients, Table 3 & Supplemental
Figure 3) and again less for the CPNB group compared to multimodal analgesia (MD -1.41 days [95%
CI -2.45, -0.36], p=0.008, $I^2=98\%$, 8 studies, 770 patients, Table 2 & Supplemental Figure 2). PONV
was not statistically significantly different between either multimodal or epidural analgesia overall
(odds ratio (OR) 0.89 [95% CI 0.72, 1.10], p=0.30, $I^2=0\%$, 7 studies, 568 patients; OR 1.02 [95% CI
0.56, 1.86], p=0.96, $I^2=36\%$, 5 studies, 265 patients), nor for any of the subgroups.
Sensitivity analyses

We examined the robustness of the main outcomes by conducting a series of sensitivity analyses (Supplemental Table 3). Nine studies had two or more domains that were deemed to have high risk of bias. [21-23,26-28,32,42,46] In the primary analyses, the difference in opioid consumption between CPNBs and epidural only bordered on statistical significance. However, there was a significant difference in opioid consumption favoring epidurals once high risk of bias studies were removed (MD 16.66 [95% CI 2.48, 30.84], p=0.02, I²=96%, 5 studies, 205 patients). Removing high risk of bias studies resulted in the length of stay (LOS) difference becoming non-significant between CPNB and multimodal analgesia (MD -1.57 days [95% CI -3.61, 0.48], p=0.13, I²=88%, 6 studies, 570 patients). Other outcomes were minimally affected by removing high risk of bias studies.

The only two studies that included patients with a lower midline incision were removed to examine the effect. [30,42] Removing these studies had minimal effect on the pain scores, PONV, opioid consumption, or LOS. The two cohort studies comparing CPNBs to multimodal analgesia were removed to examine the effect. [31,32] Removing cohort studies had minimal effect on pain scores, PONV, and opioid consumption. However, the difference in LOS became a statistical non-significant result (MD -1.29 days [95% CI -3.16, 0.57] p=0.17, I²=94%, 7 studies, 670 patients).

Eight studies [21,22,26,27,34,43-45] used opioids in the epidural solution while four studies [24,29,36,46] used only local anesthetic. Removing the studies that did not use opioids in the epidural solution did not change the effect size of pain scores but changed the results to a statistically
significant one (MD 0.48 [95% CI 0.34, 0.61], p<0.001, I²=0%, 4 studies, 216 patients). There was only one study which explicitly stated the epidural opioids were included in the calculation of cumulative opioid consumption. [26] Removing these studies reduced the effect size of opioid consumption between CPNB and epidural analgesia (MD 4.48mg [95% CI -14.95, 23.91mg], p=0.65, I²=93%, 4 studies, 183 patients). Removing these studies had minimal effect on length of stay and PONV rates.

Discussion

The use of continuous peripheral nerve blocks, often in the form of fascial plane blocks, is increasingly common. [47] The popularity of these techniques has grown in response to the potential complications and drawbacks of neuraxial analgesia such as hypotension from sympathetic blockade, leg weakness, epidural hematomas and epidural abscesses. [47] However, many of these techniques are relatively new and their efficacy has not been established relative to epidural analgesia, opioid analgesia or to each other.

We found that pain scores were not significantly different when comparing the combined effect of all CPNBs to either multimodal or epidural analgesia for abdominal surgery via a midline laparotomy. Our meta-analysis found that opioid consumption was significantly less for CPNBs compared to conventional analgesia with opioids, particularly for wound, preperitoneal, and rectus sheath catheters. There was no significant difference in opioid consumption when comparing CPNBs as a whole to epidural analgesia. However, opioid consumption was significantly less for patients receiving epidural analgesia when compared to preperitoneal, rectus sheath and paravertebral catheters. In a number of cases, this review states that there are no significant differences between CPNBs and either multimodal
or epidural analgesia. This does not necessarily imply equivalency between the two techniques, but rather insufficient data to suggest superiority of one technique over the other. This is particularly true when a small number of studies are used in the comparison. Although meta-analysis seeks to increase statistical power by combining studies, the power may decrease when a small number of studies are included. Because the random effects model accounts for between-study variation, 5 or more studies are required to reliably achieve greater power than the primary studies. [48]

Overall, the main findings of this review were robust, being only minimally influenced by the sensitivity analyses. Removing studies with procedures using lower midline incisions did not significantly change the results of the meta-analyses. When studies with two or more high risk of bias domains were removed the opioid consumption, comparison moved from bordering on statistical significance to favouring epidurals; however, the change in effect size between groups was negligible. Length of stay was the most sensitive to removing high risk studies. When high risk of bias and cohort studies were removed the difference in length of stay became not statistically significant with the point estimate moving in the opposite direction.

One area of concern is that we were not able to determine whether most studies included opioids administered via the epidural route into the calculation of total cumulative opioid consumption. This was only explicitly stated in one study. This may have a large impact on whether one technique is favoured over another in terms of opioid reduction for a few reasons. Although there is some uncertainty about equianalgesic dose conversion from IV systemic to epidural opioids, the most commonly cited conversion is 10:1 for both morphine and hydromorphone. [49] Thus, even low dose opioids added to epidural solutions can contribute to a large proportion of the cumulative opioid
consumption. Furthermore, the patients would receive this amount of opioid whether they needed it or not. This creates a conflict for pain research because including epidural opioids in the cumulative opioid consumption will favour other techniques, while not including them will favour epidurals. Our recommendation is future studies comparing CPNB to epidural analgesia use only local anesthetic without opioids in the epidural solution if using opioid consumption as an outcome. The next best option is to be very explicit in the method of equianalgesic opioid conversion from the epidural solution to the cumulative opioid consumption.

The majority of studies in this review had at least one domain that was deemed to have high potential for bias. Our ability to draw firm conclusions from this review was hampered by this high risk of bias. However, removing the studies with 2 or more domains of high risk of bias did not influence the pain score comparison. The finding that epidurals may reduce opioids more than CPNBs was strengthened when removing these studies, and the finding that CPNBs may reduce length of stay compared to multimodal analgesia was lessened. Overall, if bias was influencing the results of studies, it seems to exaggerate the benefits of CPNBs in our included studies.

In addition to risk of bias our ability to draw conclusions was limited by heterogeneity. There was some clinical heterogeneity between studies due to various types of surgery and practice patterns regarding the type and dose of analgesics and adjuncts. However, pooled results for pain scores and opioid consumption were deemed acceptable by our team since the bulk of postoperative pain originates from the abdominal wall. [50] All included studies involved a midline incision and each intervention was aimed at reducing afferent nociceptive signaling from the thoracoabdominal nerves. There was also statistical heterogeneity found in many of our analyses. This was expected given the
practice variation in terms of pain management and uses of adjunct therapies. The heterogeneity seen in terms of pain and opioid consumption also relates strongly to the type of surgery. Despite these differences, pooled results were deemed acceptable given that in each case the two comparison groups were undergoing the same surgical procedure and were subject to the same pain management practice patterns. Ideally, we would have compared various CPNB techniques to one another using a network meta-analysis. We contemplated this but decided that given the degree of clinical and statistical heterogeneity described above the assumptions of transitivity and consistency would not be met.

Conclusions and Implications

This review did not find evidence of superior pain scores between continuous peripheral nerve blockades (CPNBs) and either multimodal or epidural analgesia. CPNBs may decrease postoperative opioid consumption and hospital length of stay compared to multimodal analgesia. Epidural analgesia may further decrease opioid consumption and length of stay when compared to CPNBs. CPNBs should be considered a viable alternative to epidural analgesia when contraindications to epidural placement exists for patients undergoing midline laparotomies. Future studies should directly compare various CPNB techniques to each other. Future systemic reviews should seek to directly or indirectly compare various CPNB techniques once enough high-quality studies allow assumptions to be met.
References

29. Yassin MH, Elmoneim TAA, Moutaz HE. The Analgesic Efficiency of Ultrasound-Guided Rectus Sheath Analgesia Compared with Low Thoracic Epidural Analgesia After Elective
Abdominal Surgery with a Midline Incision: A Prospective Randomized Controlled Trial. Anesth Pain Med 2017; 7.


Table 1. Characteristics of included studies comparing continuous peripheral nerve blockade (CPNB) to usual care and epidural analgesia for patients undergoing midline laparotomy.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>n</th>
<th>Age mean (SD) years</th>
<th>Sex % (male)</th>
<th>BMI mean (SD) m2/kg</th>
<th>CPNB type</th>
<th>Placed by</th>
<th>Local anesthetic</th>
<th>Infusion (ml/hr)</th>
<th>Intermittent (ml X hours)</th>
<th>Surgical procedure</th>
</tr>
</thead>
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<td>Surgeon</td>
<td>Ropi 0.5%</td>
<td>4ml/hr</td>
<td>n/a</td>
<td>Colorectal</td>
</tr>
<tr>
<td>Wang 2010</td>
<td>Australia</td>
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<td>27 65 23 70 22</td>
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<td>Surgeon</td>
<td>Ropi 0.2%</td>
<td>4ml/hr</td>
<td>n/a</td>
<td>Colorectal</td>
</tr>
<tr>
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<td>China</td>
<td>25</td>
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<td>64 68</td>
<td>23 2 23 4</td>
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<td>Surgeon</td>
<td>Ropi 0.3%</td>
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<td>Gastrectomy</td>
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<tr>
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<td>Surgeon</td>
<td>Preperitoneal</td>
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<td>10ml/hr</td>
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<tr>
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<td>21 50 10 62 9</td>
<td>67 52</td>
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<tr>
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<td>Surgeon</td>
<td>Preperitoneal</td>
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<tr>
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<td>Surgeon</td>
<td>Preperitoneal</td>
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<td>6ml/hr</td>
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<tr>
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<td>Preperitoneal</td>
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<tr>
<td>Ozturk 2011</td>
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<tr>
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<td>Surgeon</td>
<td>Preperitoneal</td>
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<tr>
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<td>Finland</td>
<td>17</td>
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<td>Rectus</td>
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<td>Rectus</td>
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<td>n/a</td>
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<td>6 62 10 61 14</td>
<td>25 33</td>
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<td>Rectus</td>
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<td>36 8 36 8</td>
<td>TAP</td>
<td>Surgeon</td>
<td>TAP</td>
<td>Ropi 0.2%</td>
<td>8-10ml/hr</td>
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<tr>
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<td>Anesthesia</td>
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<td>8-10ml/hr</td>
<td>n/a</td>
<td>Multiple</td>
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<td>B. Epidural</td>
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<td>25</td>
<td>25 68 12 62 18</td>
<td>36 44</td>
<td>NR NR NR NR</td>
<td>Wound</td>
<td>Surgeon</td>
<td>Ropi 0.3%</td>
<td>5ml/hr</td>
<td>n/a</td>
<td>Gastroctomy</td>
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<tr>
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<td>36 44</td>
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<td>Preperitoneal</td>
<td>Surgeon</td>
<td>Preperitoneal</td>
<td>Ropi 0.2%</td>
<td>10ml/hr</td>
<td>n/a</td>
</tr>
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<td>Surgeon</td>
<td>Preperitoneal</td>
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<td>4ml/hr</td>
<td>n/a</td>
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<tr>
<td>El Feky 2014</td>
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<td>28</td>
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<td>Preperitoneal</td>
<td>Bupi 0.25%</td>
<td>10ml/hr</td>
<td>n/a</td>
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<tr>
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<td>Surgeon</td>
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<td>Bupi 0.2%</td>
<td>10ml/hr</td>
<td>n/a</td>
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<tr>
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<td>Surgeon</td>
<td>Preperitoneal</td>
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<td>n/a</td>
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<tr>
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<td>Anesthesia</td>
<td>TAP</td>
<td>Bupi 0.5%</td>
<td>8ml/hr</td>
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<tr>
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<td>31 4 31 3</td>
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<td>Anesthesia</td>
<td>TAP</td>
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<td>Anesthesia</td>
<td>Rectus</td>
<td>Bupi 0.25%</td>
<td>20ml q8hr</td>
<td>n/a</td>
</tr>
<tr>
<td>Hutchins 2018</td>
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<td>23 68 12 64 9</td>
<td>48 61</td>
<td>NR NR NR NR</td>
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<td>Anesthesia</td>
<td>Paravertebral</td>
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<tr>
<td>Sondekoppam 2019</td>
<td>Canada</td>
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<td>34 60 14 62 13</td>
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<td>28 6 27 5</td>
<td>Paravertebral</td>
<td>Paravertebral</td>
<td>Paravertebral</td>
<td>Ropi 0.2%</td>
<td>7ml/hr</td>
<td>n/a</td>
</tr>
</tbody>
</table>
Table 2. Summary of findings for continuous peripheral nerve block (CPNB) compared to usual care for patients undergoing surgery via midline laparotomy.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect</th>
<th>No of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain assessed with: Numeric Rating Scale (NRS)</td>
<td>The mean pain was 2.1</td>
<td>MD 0.35 lower (0.77 lower to 0.07 higher)</td>
<td>909 (9 RCTs, 1 Cohort)</td>
<td>★★★◯◯ LOW † ‡</td>
<td>The evidence suggests that CPNB results in little to no difference in pain.</td>
</tr>
<tr>
<td>Opioid consumption assessed with: Oral Morphine Equivalents (OME)</td>
<td>The mean opioid consumption was 92.9 mg</td>
<td>MD 31.52 mg lower (42.81 lower to 20.22 lower)</td>
<td>970 (11 RCTs, 2 Cohorts)</td>
<td>★★★◯◯ LOW † ‡</td>
<td>The evidence suggests CPNB reduces opioid consumption.</td>
</tr>
<tr>
<td>Length of hospital stay assessed with: Days</td>
<td>The mean length of hospital stay was 7.2 days</td>
<td>MD 1.41 days lower (2.45 lower to 0.36 lower)</td>
<td>770 (7 RCTs, 1 Cohort)</td>
<td>★★★◯◯ LOW † ‡</td>
<td>The evidence suggests CPNB reduces length of hospital stay.</td>
</tr>
<tr>
<td>Postoperative Nausea and Vomiting (PONV)</td>
<td>127 per 1,000</td>
<td>113 per 100 (91 to 140)</td>
<td>1,000</td>
<td>RR 0.89 (0.72 to 1.10)</td>
<td>568 (7 RCTs)</td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; MD: Mean difference; OR: Odds ratio

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**Patient or population:** patients undergoing surgery via midline laparotomy  
**Intervention:** CPNB  
**Comparison:** Usual care

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>№ of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
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</thead>
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<tr>
<td>Risk with usual care</td>
<td>Risk with CPNB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**GRADE Working Group grades of evidence**

- **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty:** 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 certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- **Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect.

**Explanations**

† The majority of included studies had at least one high risk of bias domain  
‡ There was statistically significant heterogeneity
Table 3. Summary of findings for continuous peripheral nerve block (CPNB) compared to epidural analgesia for patients undergoing surgery via midline laparotomy.

<table>
<thead>
<tr>
<th>Patient or population</th>
<th>CPNB</th>
<th>Epidural analgesia</th>
</tr>
</thead>
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<tr>
<td><strong>Intervention</strong></td>
<td>CPNB</td>
<td>Epidural analgesia</td>
</tr>
<tr>
<td><strong>Comparison</strong></td>
<td>Epidural analgesia</td>
<td>Epidural analgesia</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects' (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Ne of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain assessed with:</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Numeric rating scale (NRS)</td>
<td>The mean pain was 1.8</td>
<td>MD 0.45 higher (0.13 lower to 1.04 higher)</td>
<td>-</td>
<td>375 (8 RCTs)</td>
<td>LOW † †</td>
</tr>
<tr>
<td></td>
<td>The evidence suggests CPNB results in little to no difference in pain.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid consumption assessed with: Oral Morphine Equivalents (OME)</td>
<td>The mean opioid consumption was 35.4 mg</td>
<td>MD 16.13 mg higher (0.10 lower to 32.36 higher)</td>
<td>-</td>
<td>342 (8 RCTs)</td>
<td>LOW † †</td>
</tr>
<tr>
<td></td>
<td>The evidence suggests epidural analgesia decreases opioid consumption slightly compared to CPNB.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of hospital stay assessed with: Days</td>
<td>The mean length of hospital stay was 5.7 days</td>
<td>MD 0.78 days higher (0.27 higher to 1.29 higher)</td>
<td>-</td>
<td>399 (8 RCTs)</td>
<td>LOW † †</td>
</tr>
<tr>
<td></td>
<td>The evidence suggests epidural analgesia decreases length of hospital stay compared to CPNB.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative nausea and vomiting (PONV)</td>
<td>103 per 1,000</td>
<td>104 per (60 to 175)</td>
<td>1,000</td>
<td>OR 1.02 (0.56 to 1.86)</td>
<td>265 (5 RCTs)</td>
</tr>
<tr>
<td></td>
<td>CPNB likely results in little to no difference in postoperative nausea and vomiting (PONV) compared to epidural analgesia.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; MD: Mean difference; OR: Odds ratio

<table>
<thead>
<tr>
<th>GRADE</th>
<th>Working Group grades</th>
<th>Certainty of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>High certainty:</td>
<td>We are very confident that the true effect lies close to the estimate of the effect, but there is a possibility that it is substantially different from the estimate of the effect</td>
<td></td>
</tr>
<tr>
<td>Moderate certainty:</td>
<td>We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect</td>
<td></td>
</tr>
<tr>
<td>Low certainty:</td>
<td>Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect</td>
<td></td>
</tr>
<tr>
<td>Very low certainty:</td>
<td>We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect</td>
<td></td>
</tr>
</tbody>
</table>

Explanations

† The majority of included studies had at least one high risk of bias domain.
‡ There was statistically significant heterogeneity
Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of included studies.
Figure 2. Cumulative opioid consumption (in oral morphine equivalents) at 48 hours comparing between continuous peripheral nerve blocks (CPNB) and multimodal analgesia for midline laparotomy patients.

Legend: 95% CI = 95% confidence interval, IV = inverse variance, PCA = patient-controlled analgesia, green color = low risk of bias, yellow color = unclear/moderate risk of bias, red color = high risk of bias
Figure 3. Cumulative opioid consumption (in oral morphine equivalents) at 48 hours comparing between continuous peripheral nerve blocks (CPNB) and epidural analgesia for midline laparotomy patients.

Legend: 95% CI = 95% confidence interval, IV = inverse variance, green color = low risk of bias, yellow color = unclear/moderate risk of bias, red color = high risk of bias
### Supplemental Table 1: Search strategy for Embase, Cochrane and MEDLINE databases.

<table>
<thead>
<tr>
<th>Embase</th>
<th>Cochrane</th>
<th>MEDLINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>'laparotomy'/exp OR</td>
<td>(laparotomy or 'anastomosis, surgical' or 'gastric bypass' or gastoplasty or 'jejunoileal bypass')</td>
<td>exp Laparotomy/ or exp Anastomosis, Surgical/ or exp Gastric bypass/ or exp Gastroplasty/ or exp Jejunoileal</td>
</tr>
<tr>
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</tr>
<tr>
<td>'jejunoileal bypass'/exp OR</td>
<td>'pelvic exenteration' or splenectomy or (jejunoileal NEAR/2 bypass)</td>
<td>Surgical Procedures/ or exp Surgical Procedures/ or exp Digestive System</td>
</tr>
<tr>
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<td>'colorectal surgery' or 'general surgery'</td>
<td>'colorectal surgery' or 'general surgery' or prostatectomy:ti,ab,kw</td>
</tr>
<tr>
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<td>'surgery' or cystectomy or nephrectomy or prostatectomy:ti,ab,kw</td>
<td>Pelvic Exenteration/ or exp Splenectomy/ or exp Colorectal Surgery/ or exp General Surgery/ or exp Cystectomy/ or exp Prostatectomy/</td>
</tr>
<tr>
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<td>cystotomy or nephrectomy or prostatectomy:ti,ab,kw</td>
<td>Cystotomy/ or exp Nephrectomy/ or exp Prostatectomy/</td>
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<td>prostatectomy:ti,ab,kw</td>
<td>Cystotomy/ or exp Nephrectomy/ or exp Prostatectomy/</td>
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<td>'general surgery'/exp OR</td>
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<td>Cystotomy/ or exp Nephrectomy/ or exp Prostatectomy/</td>
</tr>
<tr>
<td>'nephrectomy'/exp OR</td>
<td>prostatectomy:ti,ab,kw</td>
<td>Cystotomy/ or exp Nephrectomy/ or exp Prostatectomy/</td>
</tr>
<tr>
<td>'prostatectomy'/exp</td>
<td>(laparotomy or 'surgical anastomosis' or 'gastric bypass' or gastoplasty or (jejunoileal NEAR/2 bypass) or (jejunoileal NEAR/2 bypass):ti,ab,kw)</td>
<td>(Laparotomy or Surgical anastomosis or Gastric bypass or Gastroplasty or (Jejunoileal adj2 bypass) or (Jejunoileal adj2 bypass):ti,ab,kw)</td>
</tr>
<tr>
<td>laparotomy:ab,ti OR 'surgical anastomosis':ab,ti OR 'gastric bypass':ab,ti OR gastoplasty:ab,ti OR (jejunoileal NEAR/2 bypass):ab,ti OR 'pelvic exenteration':ab,ti OR bypass:ab,ti OR surgery:ab,ti OR (general adj2)</td>
<td>(Laparotomy or Surgical anastomosis or Gastric bypass or Gastroplasty or (Jejunoileal adj2 bypass) or (Jejunoileal adj2 bypass):ti,ab,kw)</td>
<td></td>
</tr>
<tr>
<td>bypass:ab,ti OR</td>
<td>(jejunoileal NEAR/2 bypass)</td>
<td>(jejunoileal NEAR/2 bypass):ti,ab,kw)</td>
</tr>
<tr>
<td>gastoplasty:ab,ti OR</td>
<td>bypass) or 'pelvic exenteration' or surgery) or (general near/2</td>
<td>(jejunoileal NEAR/2 bypass) or pelvic exenteration) or surgery) or (general adj2)</td>
</tr>
</tbody>
</table>
Embase
exenteration':ab,ti OR
splenectomy:ab,ti OR
(colorectal NEAR/2 surgery):ab,ti OR
NEAR/2 surgery):ab,ti OR
cystectomy:ab,ti OR
cystotomy:ab,ti OR
nephrectomy:ab,ti OR
prostatectomy:ab,ti
((bariatric OR abdomin* OR abdomen* OR aort* OR gastric* OR gastro*) NEAR/1 (surger* OR operation*)):ab,ti
((bariatric or abdomin* or abdomen* or aort* or gastric* or gastro*) adj1 (surger* or operation*)).ti,ab,kw.
'regional anesthe*':ab,ti OR
(nerve NEAR/2 block):ab,ti
OR (local NEAR/2 anesthe*):ab,ti
Cochrane
surgery) or cystectomy or
cystotomy or nephrectomy or
prostatectomy):ti,ab,kw
Surgery) or Cystectomy or
Cystotomy or Nephrectomy or
Prostatectomy).ti,ab.kw.
MEDLINE
Surgery) or Cystectomy or
Cystotomy or Nephrectomy or
Prostatectomy).ti,ab.kw.

'local anesthetic agent'/exp
'local anesthetic agent'/exp
local):ti,ab,kw
Anesthetics, Local/
'regional anesthe*':ab,ti OR
(nerve NEAR/2 block):ab,ti
OR (local NEAR/2 anesthe*):ab,ti
('conduction anesthe*' or 'local
near/2 anesthe*' or (nerve near/2
block)):ti,ab,kw
((Conduction adj Anesthe*) or
(Nerve adj2 Block) or (Local
adj2 Anesthe*)).ti,ab,tw.
<table>
<thead>
<tr>
<th><strong>Embase</strong></th>
<th><strong>Cochrane</strong></th>
<th><strong>MEDLINE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>(((‘transversus abdominis plane’ OR tap OR paravertebral OR ‘transversalis fascia’ OR ‘quadratus lumborum’ OR rectus) NEAR/2 block*):ab,ti</td>
<td>(((‘transversus abdominis plane’) OR TAP or paravertebral or ‘transversalis fascia’) or (quadratus near/1 lumborum) or (wound or intraperitoneal or peritoneal or rectus) near/2</td>
<td>(((Transversus adj abdominis adj plane) OR TAP or Paravertebral or (Transversalis adj fascia) or (quadratus adj lumborum) or (Wound or intraperitoneal or peritoneal or rectus) adj2 block*).ti,ab,kw</td>
</tr>
<tr>
<td>(wound OR intraperitoneal OR peritoneal OR rectus) NEAR/2 (infiltration OR infusion*)):ab,ti</td>
<td>(wound or intraperitoneal or peritoneal or rectus) near/2</td>
<td>(infiltration or infusion*)).ti,ab,kw</td>
</tr>
<tr>
<td>‘elastomeric pump’:ab,ti</td>
<td>(‘elastomeric pump’):ti,ab,kw</td>
<td>(Elastomeric adj pump).ti,ab,tw</td>
</tr>
<tr>
<td>#1 OR #2 OR #3</td>
<td>#1 or #2 or #3</td>
<td>1 or 2 or 3</td>
</tr>
<tr>
<td>#4 OR #5 OR #6 OR #7 OR #8</td>
<td>#4 or #5 or #6 or #7 or #8</td>
<td>4 or 5 or 6 or 7 or 8</td>
</tr>
<tr>
<td>#9 AND #10</td>
<td>#9 and #10</td>
<td>9 and 10</td>
</tr>
<tr>
<td>#11 AND [humans]/lim</td>
<td>animals not humans</td>
<td>Limit 11 to animals</td>
</tr>
<tr>
<td></td>
<td>#11 not #12</td>
<td>11 not 12</td>
</tr>
</tbody>
</table>

**Supplemental Table 2:** OpenGrey search strategy (adapted from Medline search).
(((Subject:general surgery) OR (subject:anastomosis, surgical) OR (subject:gastric bypass) OR (subject:gastroplasty) OR (subject:jejunoileal bypass) OR (subject:digestive system surgical procedures) OR (subject:pelvic excenteration) OR (subject:splenectomy) OR (subject:colorectal surgery) OR (subject:cystectomy) OR (subject:cystotomy) OR (subject:nephrectomy) OR (subject:prostatectomy) OR laparotomy OR (surgical anastomosis) OR (gastric bypass) OR gastroplasty OR splenectomy OR colorectal surgery OR cystectomy OR nephrectomy OR prostatectomy OR (bariatric surgery) OR (bariatric operation*) OR (abdomin* surgery) OR (abdomin* operation*) OR (abdomen* surgery) OR (abdomen* operation*) OR (aort* surgery) OR (aort* surgery) OR (gastric surgery) OR (gastric operation*) OR (gastro* surgery) OR (gastro* operation*)) AND ((Subject:anesthesia, conduction) OR (subject:nerve block) OR (subject:anesthetics, local) OR (conduction anesthe*) OR (local anesthe*) OR (nerve block) OR (transversus abdominis plane block) OR (TAP block) OR (paravertebral block) OR (transversalis fascia block) OR (quadratus lumborum block) OR (ilioinguinal block) OR (iliohypogastric block) OR (wound infiltration) OR (wound infusion*) OR (intraperitoneal infiltration) OR (intraperitoneal infusion*) OR (peritoneal infiltration) OR (peritoneal infusion*) OR (rectus infiltration) OR (rectus infusion*) OR (elastomeric pump)))
**Supplemental Table 3.** Summarized results of sensitivity analyses.

<table>
<thead>
<tr>
<th>Sensitivity analysis</th>
<th>CPNB vs Usual care</th>
<th>CPNB vs Epidural</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pain (NRS)</td>
<td>Opioid Consumption (OME)</td>
</tr>
<tr>
<td>Primary analyses (all studies included)</td>
<td>MD -0.35 [-0.77, 0.07] p=0.10, I²=95%</td>
<td>MD -31.52 mg [-42.81, -20.22] p&lt;0.00001, I²=93%</td>
</tr>
<tr>
<td>High risk of bias studies removed</td>
<td>MD -0.24 [-0.71, 0.24] p=0.33, I²=88%</td>
<td>MD -24.08 mg [-34.12, -14.04] p&lt;0.00001, I²=93%</td>
</tr>
<tr>
<td>Lower midline incision studies removed</td>
<td>MD -0.47 [-0.95, 0.02] p=0.06, I²=96%</td>
<td>MD -37.12 mg [-49.43, -24.81] p&lt;0.00001, I²=93%</td>
</tr>
<tr>
<td>Cohort studies removed</td>
<td>MD -0.25 [-0.64, 0.14] p=0.21, I²=83%</td>
<td>MD -29.88 [-42.36, -17.40] p=0.30, I²=0%</td>
</tr>
<tr>
<td>Studies not using opioids in epidural solution removed</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

95% confidence interval in brackets [], grey shaded cell represent change from primary analysis, CPNB=continuous peripheral nerve block, LOS=length of stay, MD=mean difference, n/a=not applicable, NRS=numeric rating scale, OME=oral morphine equivalents in milligrams, OR=odds ratio, PONV=postoperative nausea and vomiting
Supplemental Figure 1. Funnel plot to assess publication bias for studies comparing pain scores and cumulative opioid consumption between continuous peripheral nerve blocks (CPNB) to multimodal analgesia.

A = pain scores, B = opioid consumption

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>CPNB</th>
<th>Mean [days]</th>
<th>SD [days]</th>
<th>Total</th>
<th>Multimodal</th>
<th>Mean Difference IV, Random, 95% CI [days]</th>
<th>Risk of Bias</th>
<th>Mean Difference IV, Random, 95% CI [days]</th>
<th>Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polglase 2007</td>
<td>9</td>
<td>4.66</td>
<td>13</td>
<td>19</td>
<td>11.5</td>
<td>167</td>
<td>11.0%</td>
<td>-1.00 [-2.90, 0.90]</td>
<td>D</td>
</tr>
<tr>
<td>Wang 2010</td>
<td>0</td>
<td>0</td>
<td>21</td>
<td>0</td>
<td>27</td>
<td>Not estimable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zheng 2016 (PCA)</td>
<td>8.2</td>
<td>2.54</td>
<td>3</td>
<td>10.1</td>
<td>3.15</td>
<td>23</td>
<td>30.7%</td>
<td>-1.90 [-3.89, 0.99]</td>
<td>D</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>196</td>
<td>207</td>
<td>21.7%</td>
<td>-1.48 [-2.81, -0.06]</td>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2 = 0.00, Chisq = 0.41; df = 1 (P = 0.52); I^2 = 0%
Test for overall effect: Z = 2.04 (P = 0.04)

10.9.2 Intrapерitoneal Catheter

Bai 2006         | 9.8  | 5.52        | 35        | 10.1  | 6.65       | 35                                       | 7.5%         | -0.30 [-3.16, 2.56]                      | D             |
| Kalkbrenner 2011| 4    | 6           | 30        | 4     | 5.75       | 30                                       | 7.2%         | 0.00 [-2.97, 2.97]                      | B             |
| Subtotal (95% CI)| 0.53 | 0.45        | 14.8%     | -0.18 [-1.21, 1.91] | C     |

Heterogeneity: Tau^2 = 0.00, Chisq = 0.02; df = 1 (P = 0.89); I^2 = 0%
Test for overall effect: Z = 0.15 (P = 0.88)

10.9.3 Preperitoneal Catheter

Beauvais 2007    | 1    | 1.04        | 21        | 6.13  | 2.21       | 21                                       | 14.9%        | -5.13 [-10.67, -0.99]                   | D             |

Heterogeneity: Tau^2 = 0.09, Chisq = 54.84; df = 2 (P < 0.00005); I^2 = 98%
Test for overall effect: Z = 1.66 (P = 0.19)

10.9.4 Rectus Sheath Catheter

Purdy 2016 (initial) | 0  | 0           | 12        | 0     | 6          | Not estimable                             |              |                                           |              |

Heterogeneity: Not applicable
Test for overall effect: Not applicable

10.9.5 TAP Catheter

Fayezzadeh 2016   | 5.2  | 0.4         | 50        | 6.8   | 0.4        | 50                                       | 17.4%        | -1.60 [-1.76, -1.44]                    | D             |
| Kadum 2011       | 0    | 0           | 10        | 0     | 9          | Not estimable                             |              |                                           |              |
| Subtotal (95% CI)| 29   | 12          | 41.1%     | -1.50 [-1.66, -1.34] | C     |

Heterogeneity: Not applicable
Test for overall effect: Z = 2.04 (P = 0.04)

Total (95% CI)    | 552  | 100.0%      | -1.41 [-2.45, -0.36] |              |              |
Heterogeneity: Tau^2 = 1.62; Chisq = 424.89; df = 7 (P < 0.00001); I^2 = 98%
Test for overall effect: Z = 2.64 (P = 0.008)
Test for subgroup differences: Chisq = 1.94; df = 3 (P = 0.59); I^2 = 0%
Risk of bias variable:
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Favours [CPNB]  | Favours [Multimodal]

Supplemental Figure 2. Length of stay in hospital comparing between continuous peripheral nerve blocks (CPNB) and multimodal analgesia for midline laparotomy patients.
Supplemental Figure 3. Length of stay in hospital comparing between continuous peripheral nerve blocks (CPNB) and epidural analgesia for midline laparotomy patients.

Legend: 95% CI = 95% confidence interval, IV = inverse variance, green color = low risk of bias, yellow color = unclear/moderate risk of bias, red color = high risk of bias