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Clinical Investigation

CLINICAL INVESTIGATION

Therapeutic efficacy of intravenous lidocaine infusion compared with thoracic epidural analgesia in major abdominal surgery: a non-inferiority randomised clinical trial

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Abstract

Background: Open major abdominal surgery is one of the most risky surgical procedures for acute postoperative pain. Thoracic epidural analgesia (TEA) has been considered the standard analgesic approach. In different reports, lidocaine i.v. has been shown to have an analgesic efficacy comparable with TEA. We compared the analgesic efficacy of i.v. lidocaine with thoracic epidural analgesia using bupivacaine in patients undergoing major abdominal surgery.
Methods: In this non-inferiority clinical trial, 210 patients were randomised to thoracic epidural bupivacaine with morphine or i.v. lidocaine. Dynamic pain at 24 h after surgery was measured using a numerical pain rating scale (NPR), and morphine consumption was also measured. A difference in i.v. the lidocaine-epidural bupivacaine NPR of $\leq$1 for dynamic pain was considered a non-inferiority margin.
Results: The NPR for dynamic pain in the lidocaine group at 24 h was between 5.7 (1.8) and 5.2 (1.9) in the epidural group, with a difference of 0.53 (95% confidence interval 0.0–1.0). In the first 24 h, the average difference in morphine consumption was 1.8 mg between the i.v. lidocaine and epidural groups (95% confidence interval 1–3 mg). No differences were found in adverse events or complications associated with the procedures.
Conclusions: Intravenous lidocaine is non-inferior to thoracic epidural analgesia for acute postoperative pain control in major abdomial surgery at 24 h postoperatively.
Clinical trials registration: NCT04017013.

Keywords: acute pain; epidural analgesia; intravenous lidocaine; major surgery; morphine

Editor's key points

- Open abdominal surgery is associated with one of the highest risk of severe acute postoperative pain.
- Thoracic epidural analgesia is the standard for pain management in this surgery, but is associated with several risks and potential failure. Other therapeutic options are therefore needed.
- In this non-inferiority randomised clinical trial, the authors compared the efficacy and safety of lidocaine infusion to thoracic epidural analgesia with bupivacaine in adult patients undergoing open major abdominal surgery.
- Lidocaine infusion was non-inferior to thoracic epidural analgesia for pain at rest and dynamic pain (the most difficult to control) for up to 72 h

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postoperatively, with a suggestion of improved safety of lidocaine and adequate patient satisfaction.
- These results have broad implications for multimodal analgesic management.

Open abdominal surgery has a high risk of severe acute postoperative pain,[1] which can lead to an increased risk of respiratory and cardiovascular complications, longer hospital stays, and persistent pain.[2,3] Although multiple analgesic techniques have been proposed in recent years for postoperative pain management, thoracic epidural analgesia (TEA) remains the standard for pain management in abdominal surgery.[4,5] Although a more effective analgesic effect has been demonstrated compared with other interventions,[5] this might also increase the risk of postoperative hypotension, mobility impairment, and urinary retention, thereby delaying the process of accelerated recovery.[6] Additionally, the failure rate can be as high as 32% for TEA,[7] which restricts its systematic use, regardless of the potential complications associated with its insertion, such as haematoma, infection of the insertion site, severe hypotension, or neurologic complications.[8,9]

Lidocaine, a local anaesthetic of the amide type, has been recognised for its potential analgesic and anti-inflammatory effect when used intravenously as an infusion to manage acute and chronic pain.[10–12] Studies have reported its usefulness as an analgesic alternative in major abdominal surgery with appropriate pain control, lower opioid consumption, and shorter hospital stay.[13–15] However, compared with TEA, the evidence needs to be more consistent concerning its analgesic usefulness.[16] Systematic reviews and meta-analyses suggest that i.v. lidocaine has no clinically relevant effect at 24 h of infusion compared with placebo; however, there is insufficient evidence to determine its efficacy compared with epidural analgesia.[17]

This study aimed to evaluate the analgesic effectiveness of i.v. lidocaine infusion compared with thoracic epidural analgesia in adult patients undergoing open major abdominal surgery. The hypothesis was that i.v. lidocaine is not inferior to epidural analgesia in pain control during 24 h after surgery.

Methods

The study was a non-inferiority controlled clinical trial conducted in two different tertiary hospitals in Medellín, Colombia. The study was approved by the *Institutional Review Board* of the Faculty of Medicine of the University of Antioquia (Act 14-2018) and by the different research ethics committees of the involved institutions: Hos Alma Mater of Antioquia Hospital and University Hospital of San Vicente Foundation. The study was registered before the first patient was included in ClinicalTrials.gov (*https://clinicaltrials.gov/ct2/show/NCT04017013*). The study was conducted between February 2020 and September 2022.

Participants

The study included patients >18 yr of age scheduled for major open abdominal surgery (solid or hollow abdominal viscera surgery that requires a large incision on the patient's abdomen, longer recovery time, or both).[6,18] The exclusion criteria were the following: pregnant patients; contraindications for TEA analgesia (anticoagulation, puncture site infection, and neuroaxial malformation); arrhythmias that contraindicated i.v. lidocaine; local anaesthetic allergy; hepatic and renal failure; mechanical ventilation in the postoperative period; preoperative sepsis; chronic use of strong opioid; and patients who refused to participate in the study.

Interventions

Upon obtaining informed consent, subjects were randomly assigned to receive TEA or i.v. lidocaine infusion. After basic American Society of Anesthesiolgists (ASA) monitoring, an epidural catheter was inserted between T6 and T10 for patients assigned to TEA. The choice of epidural space depended on the surgical incision. Subsequently, its correct localisation was assessed using lidocaine 2% with 5 ml epinephrine 1:200,000 through the catheter and dermatomal temperature sensitivity test. Once its localisation was verified, infusion of bupivacaine 0.1% plus morphine 20 μg ml^{-1} at 7 ml h^{-1} was started from the intraoperative period until 3 days postoperatively. This TEA combination has been evaluated in multiple studies, such as the meta-analysis conducted by Block and colleagues,[18] which reported a higher analgesic efficacy when a long-acting anaesthetic plus epidural opioid was combined.

A bolus of lidocaine 1.5 mg kg^{-1} without epinephrine was administered to subjects assigned to the i.v. lidocaine group during anaesthetic induction, and infusion was maintained at 1 mg kg^{-1} h^{-1} infusion for 24 h. We used ideal body weight for lidocaine dose calculation.

All subjects were given a morphine schedule through a *patient-controlled analgesia* (PCA) system. Other types of analgesic medication or regional analgesia techniques, other than TEA, were not allowed for the patients.

After extubation, all subjects were transferred to a high-dependency unit for at least 24 h.

Randomisation

Randomisation was determined using a statistical program with variable permuted blocks of 4, 6, and 8, with a 1:1 ratio of TEA and i.v. lidocaine. The randomisation was concealed by blinded and opaque envelopes, respectively numbered. Both randomisation and concealment were performed by a research assistant independent of the workgroup. Once the patient was recruited, the anaesthesiologist opened the envelope and perform the procedure indicated in the envelope: 'EPIDURAL' or 'LIDOCAINE'.

Blinding

This was an open-label study as it was impossible to blind either the anaesthesiologist or the subjects, given the types of interventions evaluated. However, the outcome adjudicator and statistician were blinded to randomisation and intervention allocation.

Primary outcome

The primary outcome was dynamic pain associated with movement (getting out of bed, walking, or coughing) at 24 h after surgery. This was considered as the non-inferiority outcome. This was measured blindly using the numerical pain rating scale (NPR), with '0' being 'no pain' and '10' being the 'most intense pain possible'.

Intravenous morphine consumption at 24 h after surgery was also assessed using patient-controlled analgesia (PCA) quantification.

Secondary outcomes

Dynamic postoperative pain

Movement-evoked pain at 48 h and 72 h postoperatively using the NPR scale.

Postoperative pain at rest

Pain was measured at rest at 2, 6, 12, 48, and 72 h postoperatively.

Opioid analgesic rescue

The need for opioid analgesic rescue was measured at 2 h postoperatively.

Opioid consumption

Morphine-equivalent consumption was assessed at 48 h and 72 h postoperatively.

Postoperative satisfaction evaluation

Degree of satisfaction was assessed using the "Evaluation du Vecu de I'Anesthesie Generale" (EVAN-G) scale, which considers the quality of perioperative care. The scale was developed by Auquier and colleagues[19] with broad psychometric validity in different studies.[20] As the original scale is in French, it was validated in Spanish by Benítez-Linero and colleagues at the University of Valencia, Spain.[21] This scale was used with the author's consent.

The results were grouped into six major domains or factors of the EVAN-G scale: appropriate preoperative information; reasonable waiting times for medical care; degree of comfort in the postoperative period; postsurgical medical care; privacy and family support for the patient; and good pain control. The

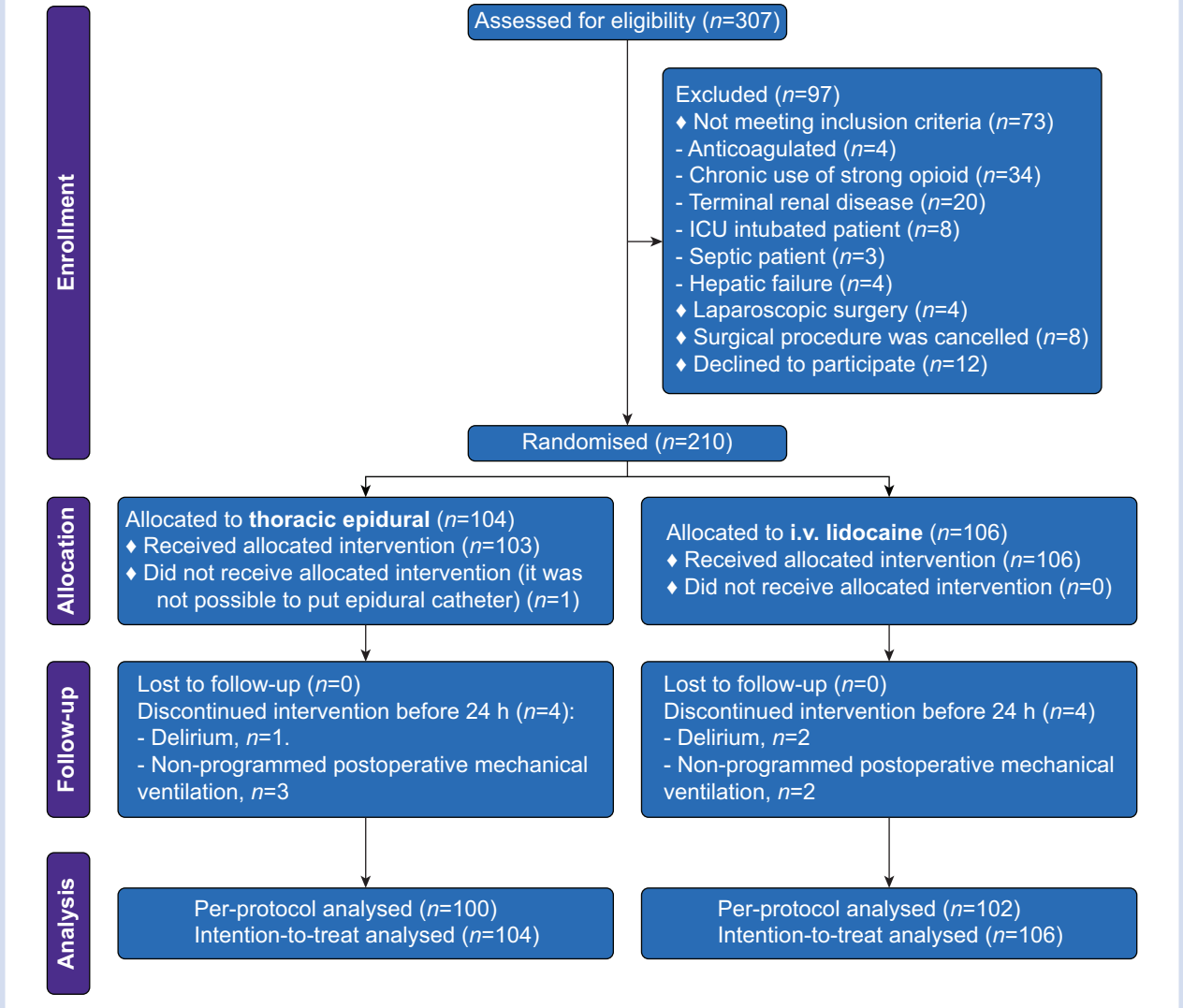

Fig 1. CONSORT flow diagram. CONSORT, Consolidated Standards of Reporting Trials.

minimum possible score was '0' and '100' was the maximum score for the evaluated factor.

Other outcomes

Haemodynamic instability with the need for postoperative vasopressor support; signs or symptoms of local anaesthetic toxicity; postoperative nausea and vomiting; degree of sedation according to the Ramsey scale; delirium; respiratory depression were evaluated 72 h after surgery. We also evaluated the postsurgical waking onset time, length of hospital stay, and death during all hospital stays.

Sample design

The sample size calculation adhered to the 2016 US Food and Drug Administration recommendations for sample design of non-inferiority trial studies for drugs and medical devices.[22] Based on these recommendations, the fixed-margin method proposed by Rothmann and colleagues[23] was used to select the non-inferiority delta.[22] Initially, the meta-analysis performed by Block and colleagues[18] was used as a reference. From the latter, clinical trials that assessed the performance of epidural analgesia *vs* parenteral opioid administration in abdominal surgery were included and added to determine the M1 (first margin), representing the clinical effect of the analgesic reference technique for these surgical models.[24–28] For this purpose, a meta-analytical summary of the studies was established, showing the outcome of pain 24 h later using the NPR.[18,24–28] A minimal difference (M1) was found between epidural *vs* PCA (1.58) (mean difference of 1.9, 95% confidence interval [CI]=−2.2 to −1.6).

During the second stage, an M2 (second margin) was defined using the Delphi methodology together with the pain management group of the University of Antioquia, which concluded that i.v. lidocaine should retain at least 40% of the analgesic effect of the previously defined lower margin (M1) (1.58 − [1.58*0.4]=0.95 to ~1). Hence, the M2 or non-inferiority delta should be a difference in the i.v. lidocaine - epidural NPR of 1, recognised in other non-inferiority analyses.[16] Considering the above, with an alpha error of 0.05 and a power of 90%, the estimated sample size consisted of 206 subjects, 103 subjects per group. The sample size calculation was performed using the Epidat 4.0 program, Saúde Pública da Consellería de Sanidade, Galicia, Spain.

Statistical analysis

Baseline characteristics in both groups were presented using frequency and proportion measures for qualitative variables and central tendency and dispersion measures for quantitative variables. The Shapiro–Wilk test was performed on quantitative variables to determine the presumption of normality. In the case of normality, mean and standard deviation were reported; otherwise, median and inter-quartile range were reported.

Continuous variables were analysed using unpaired Student's *t*-test for the mean difference in case of normality; in its absence, the Mann–Whitney *U*-test was made. As this was a randomised trial with a large sample (n>30), central limit theorem assumptions were made for the primary outcome. The categorical data were analysed using Fisher's precise test for relative risks. All parameters are presented with their respective 95% CIs. The *P*-value was considered statistically significant at <0.05. No subgroup analyses were made.

The non-inferiority was declared if the upper CI limit of the difference between the NPR of the lidocaine i.v. and TEA groups is less than or equal to the established delta value, that is, 1. If this limit was higher than the delta, non-inferiority could not be declared.

For the primary outcome, we performed a per-protocol analysis. As this was a non-inferiority study, the conclusions of the primary outcome were drawn according to the per-protocol population, which is determined by the subjects who completed at least 80% of the scheduled treatment time under the assigned group (80% of the 24 h time treatment after surgery) and who have not been admitted to the intensive care unit under mechanical ventilation in an unplanned fashion. However, we performed an intention-to-treat sensitivity analysis to assess the robustness of per-protocol results for primary outcomes. For the other outcomes, an intention-to-treat analysis was performed.

All analyses were performed using R statistical software version 4.2.1 (R foundation for statistical computing, Vienna, Austria).

Table 1 Patients' characteristics.

Variable	Lidocaine (n=106)	Epidural (n=104)
Sex, *n* (%)		
- Female	53 (50)	54 (51.9)
- Male	53 (50)	50 (48.1)
Age (yr), median [IQR]	59.5 [49.5–71]	59 [53–73]
Height (cm), median [IQR]	163 [155–170]	160 [155–165]
Weight (kg), median [IQR]	64 [55–64]	64.5 [55–75]
ASA physical status, *n* (%)		
1	4 (3.8)	0 (0)
2	39 (36.8)	36 (34.6)
3	63 (59.4)	68 (59.4)
Comorbidities, *n* (%)		
- Hypertension	42 (39.6)	39 (37.5)
- Diabetes mellitus	18 (17)	16 (15.4)
- Chronic kidney disease	3 (2.8)	5 (4.8)
- Chronic heart failure	1 (0.9)	2 (1.9)
- Chronic obstructive pulmonary disease	3 (2.8)	11 (10.6)
- Anaemia	5 (4.7)	6 (5.8)
- Obesity	2 (1.9)	7 (6.7)
- Hypothyroidism	5 (4.7)	8 (7.7)
- Cancer	54 (50.9)	66 (63.5)
Type of surgery, *n* (%)		
- Biliary surgery	33 (31.1)	15 (14.4)
- Hemicolectomy	23 (21.7)	16 (15.4)
- Gastrectomy	15 (14.2)	13 (12.5)
- Pancreatoduodenectomy	14 (13.2)	31 (29.8)
- Gastrointestinal fistula closure	5 (4.7)	11 (10.6)
- Open cholecystectomy	6 (5.7	4 (3.8)
- Hepatectomy	3 (2.8)	8 (7.7)
- Retroperitoneal tumour resection	2 (1.9)	5 (4.8)
- Open nephrectomy	3 (2.8)	1 (1)
- Open ileostomy	1 (0.9)	0
- Splenectomy	1 (0.9)	0
Hospital centre, *n* (%)		
- Hospital Alma Mater of Antioquia	63 (59.4)	63 (60.6)
- San Vicent's University Hospital	43 (40.6)	41 (39.4

ASA, American Society of Anesthesiologists; IQR, inter-quartile range.

Results

Between February 2020 and September 2022, the eligibility criteria were evaluated in 307 patients at the Hospital Alma Mater of Antioquia and University Hospital San Vincent's Foundation. A total of 210 subjects were randomly assigned to the TEA or i.v. lidocaine group (see CONSORT flowchart in Figure 1). Only one subject was unable to have an epidural catheter insertion. Before 24 h postoperatively, the assigned intervention was suspended in eight subjects (3.8%), four in the epidural group and four in the lidocaine group, five of whom required unplanned mechanical ventilation and the other three subjects developed delirium in the first 24 h. After 24 h, three subjects in the epidural group had epidural catheter dysfunction, and the procedure was terminated. No subject follow-up was discontinued.

The baseline characteristics of the subjects by intervention group are presented in Table 1.

Regarding the primary outcome, the dynamic pain 24 h after surgery showed a mean NPR of 5.7 (1.8) for the i.v. lidocaine group compared with 5.2 (1.9) for the epidural group, with a difference between groups of 0.5 (95% CI 0.0–1.00). As for static pain, 24 h after surgery, the difference between groups was 0.5 (95% CI −0.1 to 0.9). Table 2 and Figure 2 show the other estimates and intervals for the different periods assessed for both dynamic and resting pain.

Intravenous morphine equivalent opioid consumption at 24 h post-surgery for the i.v. lidocaine group was a median of 4.3 mg [inter-quartile range 2–10 mg] compared with 2.5 mg [inter-quartile range 1.2–6 mg] for the epidural group, with a median difference of 1.8 mg (95% CI 1–3 mg). Table 2 shows the cumulative opioid consumption at 48 h and 72 h.

No differences were found between per-protocol and intention-to-treat sensibility analyses in the outcomes of dynamic pain 24 h after surgery (Table 2).

Subjects in the lidocaine group had a greater need for analgesic rescue in the first 2 h postoperatively with an Relative Risk (RR) of 1.72 (95% CI 1.07–2.77). The groups had no differences in the perioperative haemodynamic instability or other safety outcomes. However, a longer anaesthesia time and longer hospital stay were noted in subjects in the lidocaine group, with an average difference of 3 days in favour of lidocaine. There were no differences in mobility time and hospital stay (Table 2).

One subject in the i.v. lidocaine group had an episode of mild local anaesthetic toxicity that was managed with the discontinuation of lidocaine infusion, requiring no supportive measures or intravenous fluids.

Regarding the results of perioperative satisfaction, no differences were found between the groups in the six domains evaluated (Table 3).

Table 2 Primary and secondary outcomes by group. *This event occurred 48 h after surgery and 24 h after the end of lidocaine infusion. †No deaths in the 3-day observation period. All 11 deaths were reported after a 3-day observation period, and none were associated with the interventions. IQR, inter-quartile range; NA, not applicable; POP, postoperative; SD, standard deviation.

Outcomes	Lidocaine (n=106)	Epidural (n=104)	Mean difference (IC 95%)	P-value
24 h dynamic pain, NPR scale; mean (SD)				
- Per-protocol population	5.7 (1.8)	5.2 (1.9)	0.5 (0.0–1.0)	
- Intention-to-treat population	5.4 (1.9)	5.5 (1.9)	0.1 (−0.5 to 0.5)	
Dynamic pain, NPR scale; mean (SD)				
- 48 h	4.7 (1.3)	4.2 (1.8)	0.5 (0–0.9)	0.033
- 72 h	3.6 (1.3)	3.3 (1.8)	0.2 (−0.2 to 0.7)	0.316
Opioid consumption (mg of morphine), median [IQR]				
- 24 h	4.3 [2–10]	2.5 [1.2–6]	1.8 (1–3)	<0.001
- 48 h	6.6 [3.5–11.5]	3.8 [0.6–6]	2.8 (1.8–4)	<0.001
- 72 h	6 [4–11]	4 [2–6]	2 (2–4)	<0.001
Pain at rest, NPR scale; mean (SD)				
- 2 h	4.4 (2.4)	3.4 (2.7)	1.0 (0.2–1.8)	0.009
- 6 h	3.6 (2.4)	2.7 (2.6)	0.9 (0.1–1.7)	0.020
- 12 h	3.2 (2.5)	2.2 (2,.6)	1.0 (0.1–1.9)	0.003
- 24 h	3.2 (1.6)	2.7 (1.7)	0.5 (−0.1 to 0.9)	0.050
- 48 h	2.4 (1.3)	2.2 (1.5)	0.2 (−0.2 to 0.6)	0.340
- 72 h	1.9 (1.2)	1.8 (1.3)	0.1 (−0.2 to 0.5)	0.490
Surgical time (min), median [IQR]	200 [150–270]	240 [160–300]	−40 (−45 to 0.9)	0.067
Anaesthetic time (min), median [IQR]	240 [200–324]	300 [230–360]	−35 (−60 to −10)	0.006
Time for first ambulation (days), median [IQR]	3 [2–3]	3 [2–3]	0 (−3.8 to 3.1)	0.891
Time of hospital stay (days), median [IQR]	7 [5–13]	10 [5.5–17]	−3 (−4 to −1)	<0.001
Perioperative complications, n (%)				
- Severe hypotension	1 (0.9)	4 (3.8)	0.24 (0.03–1.81)	0.209
- Bradycardia	0 (0)	1 (0.9)	NA	NA
- Intraoperative bleeding	3 (2.8)	4 (3.8)	0.73 (0.17–3.20)	0.720
2-h POP opioid rescue, n (%).	41 (38.7)	20 (19.2)	1.72 (1.07–2.77)	0.003
24-h haemodynamic instability, n (%)	2 (1.9)	4 (3.8)	0.72 (0.17–3.16)	0.710
POP nausea and vomiting, n (%).	20 (18.9)	25 (24)	0.78 (0.47–1.32)	0.403
24-H local anaesthetic toxicity, n (%)	1 (0.94)	0 (0)	NA	NA
Ramsay sedation scale, n (%)				
1	0 (0)	1 (0.96)	NA	NA
2	99 (93.4)	100 (96.1)	0.97 (0.91–1.03)	0.538
3	4 (3.8)	3 (2.9)	1.31 (0.30–5.70)	1.006
Respiratory depression, n (%)	1 (0.94)*	0 (0)	NA	NA
Delirium, n (%)	2 (1.9)	2 (1.9)	0.98 (0.14–6.87)	1.003
POP death, n (%)†	8 (7.4)†	3 (2.9)†	2.61 (0.75–9.09)	0.214

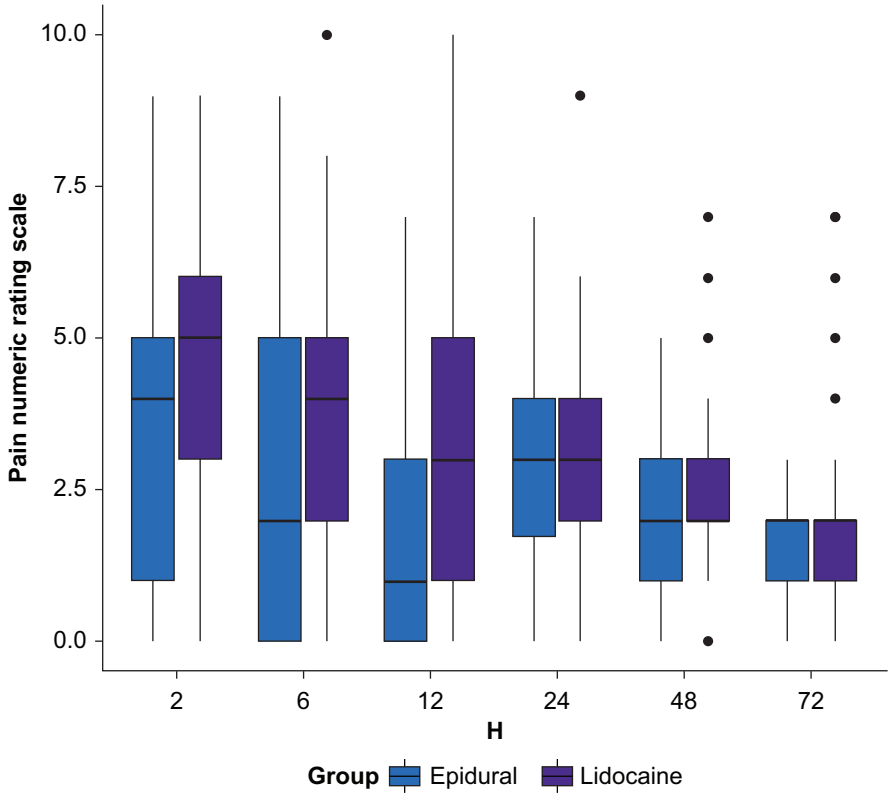

Fig 2. Numeric pain rating scale for each time interval. Boxes represent the inter-quartile range; the horizontal line is the median and the vertical line indicates min–max.

Table 3 Perioperative satisfaction. *Each factor was evaluated with 0–100 scores, with 0 points as the worst and 100 points as the best possible. SD, standard deviation.

Factor*	Lidocaine (n=106)	Epidural (n=104)	P-value
Preoperative information, mean (SD)	77.5 (20.5)	79.3 (19.8)	0.518
Acceptable surgical waiting times, mean (SD)	48.4 (14.6)	50.1 (15.2)	0.409
Perioperative comfort, mean (SD)	67.5 (12.2)	67.5 (11.8)	1.000
Postoperative medical attention, mean (SD)	93.2 (12.5)	91 (14.4)	0.238
Privacy, mean (SD)	63 (12.0)	61.4 (10.4)	0.303
Pain control, mean (SD)	71.7 (10.9)	75.6 (10.4)	0.086

Discussion

This clinical trial demonstrated that lidocaine infusion was non-inferior to thoracic epidual analgesia in the average assessment of dynamic pain at 24 h after surgery in patients who underwent open major abdominal surgery. We found similar results at 48 h and 72 h postoperatively (Fig. 3).

While no margin of non-inferiority for opioid consumption was established beforehand, a difference in morphine consumption at 24 h (~2 mg) does not seem relevant and supports the non-inferiority hypothesis.

Although after 24 h, pain control, both dynamic and at rest, was similar in both groups, consistent differences during the first postoperative hours favoured the epidural technique. This explains the increased need for analgesic rescue in subjects who received lidocaine infusion in the first postoperative hours. These results are consistent with other studies that report significant analgesic differences favourable to the epidural technique in the first hours postoperatively.[16,29,30] Indeed, the systematic review and meta-analysis conducted by Weibel and colleagues[17] showed that the best analgesic control by epidurals is observed in the first 4 h postoperatively compared with i.v. lidocaine, a difference that is not maintained beyond 12 h postoperatively.

The present study was designed to show non-inferiority of i.v. lidocaine compared with TEA in patients who underwent major open abdominal surgery. Although Terkawi and colleagues[16] performed a study comparing epidural *vs* i.v. lidocaine in these patients, with a remarkably similar sample size, this

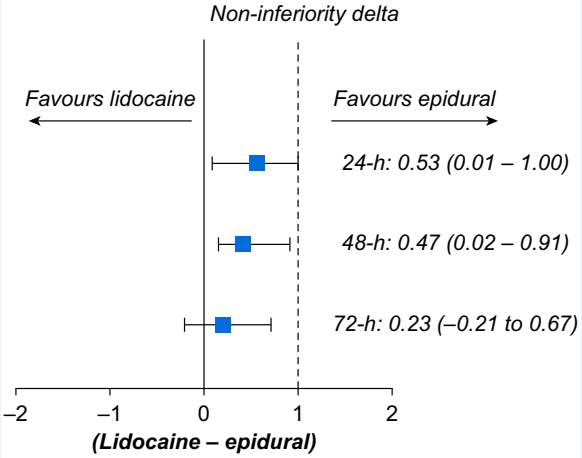

Fig 3. Non-inferiority margins for dynamic pain score. Point estimate and 95% CI. CI, confidence interval.

was a non-randomised cohort study. Furthermore, our study differentiated pain at rest from dynamic pain as the latter is more difficult to control in any surgical scenario. We found no clinically significant difference in static and dynamic pain 24 h postoperatively between groups; these results are consistent with those reported in previous clinical studies.[29–31] Similarly, when extrapolating the results beyond pain and evaluating the quality of recovery and satisfaction with perioperative management, no differences were observed in any of the satisfaction domains evaluated.

While previous studies of perioperative lidocaine infusion protocols vary in dose and duration, our study was more conservative regarding dosage and infusion time. Although lidocaine infusion was only sustained until the first 24 h postoperatively, the analgesic effect in our subjects was preserved until 72 h with no major differences in opioid consumption. In 2021, Foo and colleagues[32] published a consensus on the use of i.v. lidocaine. This recommends that i.v. lidocaine infusion should not be administered beyond 24 h because of the cumulative effect. Although our study did not determine the plasma concentrations of lidocaine, it is noteworthy that the analgesic effect is persistent up to 2 days after the infusion has been suspended, which might be explained as a possible redistributive effect of lidocaine.[11] Based on these results, it can be stated that it is not necessary to maintain lidocaine infusion for >24 h to sustain a good postoperative control in the first 3 days postoperatively.

There were more cardiovascular events in patients with TEA during and up to 24 h after the procedure (8.7% epidural *vs* 2.8% lidocaine), but this difference is not statistically significant. Nevertheless, i.v. lidocaine might decrease the risk of these events. Whereas similar studies also show this pattern, only the cohort study by Terkawi and colleagues[16] did demonstrate a decrease of almost 86% in cardiovascular event risk when lidocaine was used compared with an epidural.

The minimal risk of lidocaine toxicity found in this work can be attributed to the dose used being well below the current recommendations for i.v. lidocaine, which is 1.5 mg kg^{-1} h^{-1}.[32,33] Moreover, no serious adverse events, such as respiratory depression, delirium, or death associated with i.v. lidocaine or TEA, were reported.

In addition to the clinical results reported, subjects with epidural analgesia had longer hospital stay. Sometimes, physicians leave epidural catheters longer than 3 days, even without pain. This can explain a longer hospital stay in the epidural group compared with the lidocaine i.v. group.

This study has limitations. Firstly, this is an open-label study; it was impossible to blind the subjects and healthcare personnel involved. Nonetheless, an attempt was made to minimise the risk of bias with blinded evaluation of the outcomes. Another limitation is that some patients did not understand the opioid administration methods through PCA systems; thus, it is possible that actual opioid consumption was underestimated in both intervention groups. However, according to the results, there appears to be no correlation between lower opioid consumption and greater pain; this effect could result from the high therapeutic effectiveness of both interventions studied.

The results have broad implications in multimodal analgesic management. On the one hand, intravenous lidocaine would be an attractive analgesic strategy in accelerated recovery protocols after intra-abdominal procedures as it limits interventions, catheters, and surgical time and reduces hospital stay, among others. On the other hand, it would be an option for patients with contraindications for epidural catheter placement.

In conclusion, intravenous lidocaine was not inferior to thoracic epidural analgesia for acute postoperative pain control in patients who underwent major open abdominal surgery at 24 h after surgery. Both techniques are highly effective for acute pain control in major abdominal surgery.

Authors' contributions

Helped design the study, conduct the study, write the manuscript and approve it for publication: all authors
Analysed data: FC, MZ

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Declaration of interest

The authors declare that they have no conflicts of interest.

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References

1. Shipton E. The transition from acute to chronic post surgical pain. *Anaesth Intensive Care* 2011; **39**: 824–36
2. Couceiro T, Valença M, Lima L, De Menezes T, Raposo M. Prevalence and influence of gender, age, and type of surgery on postoperative pain. *Rev Bras Anestesiol* 2009; **59**: 314–20
3. Singh P, Saikia P, Lahakar M. Prevalence of acute postoperative pain in patients in adult age-group undergoing inpatient abdominal surgery and correlation of intensity

of pain and satisfaction with analgesic management: a cross-sectional single institute-based study. *Indian J Anaesth* 2016; **60**: 737–43
4. Capdevila X, Moulard S, Plasse C, et al. Effectiveness of epidural analgesia, continuous surgical site analgesia, and patient-controlled analgesic morphine for postoperative pain management and hyperalgesia, rehabilitation, and health-related quality of life after open nephrectomy: a prospective, randomized controlled study. *Anesth Analg* 2017; **124**: 336–45
5. Bouman E, Theunissen M, Bons S, et al. Reduced incidence of chronic postsurgical pain after epidural analgesia for abdominal surgery. *Pain Pract* 2013; **14**: 76–85
6. Hughes M, Ventham N, McNally S, Harrison E, Wigmore S. Analgesia after open abdominal surgery in the setting of enhanced recovery surgery: a systematic review and meta-analysis. *JAMA Surg* 2014; **149**: 1224–30
7. Hermanides J, Hollmann M, Stevens M, Lirk P. Failed epidural: causes and management. *Br J Anaesth* 2012; **109**: 144–54
8. Low J, Johnston N, Morris C. Epidural analgesia: first do no harm. *Anaesthesia* 2008; **63**: 1–3
9. Moen V, Dahlgren N, Irestedt L. Severe neurological complications after central neuraxial blockades in Sweden 1990-1999. *Anesthesiology* 2004; **101**: 950–9
10. Lauretti G. Mechanisms of analgesia of intravenous lidocaine. *Rev Bras Anestesiol* 2008; **58**: 280–6
11. Hermanns H, Hollmann M, Stevens M, et al. Molecular mechanisms of action of systemic lidocaine in acute and chronic pain: a narrative review. *Br J Anaesth* 2019; **123**: 335–49
12. Eipe N, Gupta S, Penning J. Intravenous lidocaine for acute pain : an evidence-based clinical update. *BJA Educ* 2016; **16**: 292–8
13. Sun Y, Li T, Wang N, Yun Y, Gan T. Perioperative systemic lidocaine for postoperative analgesia and recovery after abdominal surgery: a meta-analysis of randomized controlled trials. *Dis Colon Rectum* 2012; **55**: 1183–94
14. Swenson B, Gottschalk A, Wells L, et al. Intravenous lidocaine is as effective as epidural bupivacaine in reducing ileus duration, hospital stay, and pain after open colon resection: a randomized clinical trial. *Reg Anesth Pain Med* 2010; **35**: 370–6
15. Marret E, Rolin M, Beaussier M, Bonnet F. Meta-analysis of intravenous lidocaine and postoperative recovery after abdominal surgery. *Br J Surg* 2008; **95**: 1331–8
16. Terkawi A, Tsang S, Kazemi A, et al. A clinical comparison of intravenous and epidural local anesthetic for major abdominal surgery. *Reg Anesth Pain Med* 2016; **41**: 28–36
17. Weibel S, Jelting Y, Pace N, et al. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery in adults. *Cochrane Database Syst Rev* 2018; **6**: CD009642
18. Block B, Liu S, Rowlingson A, Cowan A, Cowan J, Wu C. Efficacy of postoperative epidural analgesia: a meta-analysis. *JAMA* 2003; **290**: 2455–63
19. Auquier P, Pernoud N, Bruder N, et al. Development and validation of a perioperative satisfaction questionnaire. *Anesthesiology* 2005; **102**: 1116–23
20. Barnett S, Alagar R, Grocott M, Giannaris S, Dick J, Moonesinghe S. Patient-satisfaction measures in anesthesia: qualitative systematic review. *Anesthesiology* 2013; **119**: 452–78
21. Benítez-Linero I. *Validación de un cuestionario de satisfacción perioperatoria (EVAN-G). [PhD thesis]*. Sevilla, Spain: Universidad de Sevilla; 2017. Available from, https://idus.us.es/handle/11441/70510. [Accessed 8 April 2018]
22. FDA resources page. Non-inferiority clinical trials to establish effectivenes guidance for industry. Available from https://www.fda.gov/media/78504/download. (accessed 12 April 2018).
23. Rothmann M, Wiens B, Chan I. Across-trials analysis methods. In: *Design and analysis of non-inferiority trials*. 1st Edn. New York (US): Chapman and Hall/CRC; 2011. p. 90–144
24. Allaire P, Messick J, Oesterling J, et al. A prospective randomized comparison of epidural infusion of fentanyl and intravenous administration of morphine by patient-controlled analgesia after radical retropubic prostatectomy. *Mayo Clin Proc* 1992; **67**: 1031–41
25. Boylan J, Katz J, Kavanagh B, Klinck J. Epidural bupivacaine-morphine analgesia versus patient-controlled analgesia following abdominal surgery. *Anesthesiology* 1998; **89**: 585–93
26. Carli F, Mayo N, Klubien K, Schricker T, Trudel J, Belliveau P. Epidural analgesia enhances functional exercise capacity and health-related quality of life after Colonic Surgery. *Anesthesiology* 2002; **97**: 540–9
27. Carli F, Trudel J, Belliveau P. The effect of intraoperative thoracic epidural anesthesia and postoperative analgesia on bowel function after colorectal surgery: a prospective, randomized trial. *Dis Colon Rectum* 2001; **44**: 1083–9
28. Steinberg R, Liu S, Wu C, et al. Comparison of ropivacaine-fentanyl patient-controlled epidural analgesia with morphine intravenous patient-controlled analgesia for perioperative analgesia and recovery after open colon surgery. *J Clin Anesth* 2002; **14**: 571–7
29. Kuo C, Jao S, Chen K, et al. Comparison of the effects of thoracic epidural analgesia and i.v. infusion with lidocaine on cytokine response, postoperative pain and bowel function in patients undergoing colonic surgery. *Br J Anaesth* 2006; **97**: 640–6
30. Staikou C, Avramidou A, Ayiomamitis G, Vrakas S, Argyra E. Effects of intravenous versus epidural lidocaine infusion on pain intensity and bowel function after major large bowel surgery: a double-blind randomized controlled trial. *J Gastrointest Surg* 2014; **18**: 2155–62
31. Wongyingsinn M, Baldini G, Charlebois P, Liberman S, Stein B, Carli F. Intravenous lidocaine versus thoracic epidural analgesia: a randomized controlled trial in patients undergoing laparoscopic colorectal surgery using an enhanced recovery program. *Reg Anesth Pain Med* 2011; **36**: 241–8
32. Foo I, Macfarlane AJR, Srivastava D, et al. The use of intravenous lidocaine for postoperative pain and recovery: international consensus statement on efficacy and safety. *Anaesthesia* 2021; **76**: 238–50
33. Cooke C, Kennedy E, Foo I, et al. Meta-analysis of the effect of perioperative intravenous lidocaine on return of gastrointestinal function after colorectal surgery. *Tech Coloproctol* 2019; **23**: 15–24

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