

RESPIRATION AND THE AIRWAY

Analgesia and pulmonary function after lung surgery: is a single intercostal nerve block plus patient-controlled intravenous morphine as effective as patient-controlled epidural anaesthesia? A randomized non-inferiority clinical trial

R. Meierhenrich^{1*}, D. Hock¹, S. Kühn¹, E. Baltes¹, B. Muehling², R. Muche³, M. Georgieff¹ and G. Gorsewski¹

¹ Department of Anaesthesiology, ² Department of Thoracic and Vascular Surgery, and ³ Institute of Biometrics, University of Ulm, Prittwitzstraße 43, 89075 Ulm, Germany

* Corresponding author. E-mail: rainer.meierhenrich@uniklnk-ulm.de

Editor's key points

- Thoracic epidural analgesia is associated with rare but potentially serious complications.
- In the setting of lung surgery single-shot intercostal block (ICB) offers an alternative modality of postoperative regional analgesia.
- This study compared PCEA with single-shot ICB combined with PCA. ICB with PCA was not as effective as PCEA with respect to postoperative pain control and pulmonary function.
- This study does not support the use of ICB rather than thoracic epidural analgesia for postoperative pain relieve in lung surgery.

Background. Thoracic epidural anaesthesia (EDA) is regarded as the 'gold standard' for postoperative pain control and restoration of pulmonary function after lung surgery. Easier, less time-consuming, and, perhaps, safer is intercostal nerve block performed under direct vision by the surgeon before closure of the thoracotomy combined with postoperative i.v. patient-controlled analgesia with morphine. We hypothesized that this technique is as effective as thoracic EDA.

Methods. The study was designed as a single-centre, open labelled, randomized non-inferiority trial. A total of 92 patients undergoing elective lung surgery were randomly assigned to the epidural ($n=47$) or intercostal group ($n=45$), and 83 patients completed the study. Pain scores, inspiratory vital capacity, forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), and peak expiratory flow rate (PEFR) were assessed during the first four postoperative days.

Results. Median treatment differences regarding pain scores at rest failed to demonstrate non-inferiority of the intercostal nerve block at the first postoperative day. Patients of the intercostal group reported significantly higher pain scores on coughing during the first and second postoperative days. The epidural group had a significantly higher median FVC, FEV1, and PEFR values on the second postoperative day. No difference was found in pulmonary complications, length of hospital stay, or in-hospital deaths.

Conclusions. In patients undergoing lung surgery, single intercostal nerve block plus i.v. patient-controlled analgesia with morphine is not as effective as patient-controlled EDA with respect to pain control and restoration of pulmonary function.

Keywords: anaesthesia, epidural; nerve block; pain, postoperative; pulmonary ventilation; thoracotomy

Accepted for publication: 31 December 2010

Postoperative pain and reduction of pulmonary function after thoracic surgery is a major clinical problem. Thoracic epidural anaesthesia (EDA) with local anaesthetic plus opioid is commonly considered to be the 'gold standard' for postoperative pain control and restoration of pulmonary function after thoracic surgery.^{1–2} However, the placement of the epidural catheter may be time-consuming and may fail, may be contra-indicated, and may have several side-effects and rare, but severe, complications.^{3–5} In the last years, a continuous paravertebral block has been shown to be an

effective alternative for postoperative pain control after thoracic surgery.^{1–7} However, easier, less time-consuming, and, perhaps, safer technique is intercostal nerve block performed by the surgeon under direct vision before closure of the thoracotomy.⁸ In contrast to the paravertebral block, intercostal nerve block is characterized by a more lateral administration of the local anaesthetic.⁹ Possibly, due to its simplicity and safety, intercostal nerve block is worldwide the most frequently used technique for post-thoracotomy pain control.¹⁰ Its potential to reduce post-thoracotomy pain

has been demonstrated in several studies.^{1 11–13} Smaller studies have compared intercostal nerve block with thoracic EDA, but inconsistent results have been reported.^{10 14–17}

We hypothesized that a single intercostal nerve block with ropivacaine plus postoperative patient-controlled i.v. morphine might be as effective as thoracic EDA with respect to postoperative pain control and pulmonary function after thoracotomy for lung surgery.

To test this hypothesis, we performed a prospective randomized clinical trial including 92 patients undergoing lateral thoracotomy for lung surgery. Since it was not the aim to demonstrate superiority of one analgesic regime, but that the single intercostal nerve block in combination with patient-controlled i.v. morphine is not worse than patient-controlled thoracic EDA, the present study was designed as a non-inferiority clinical trial according to the extension of the CONSORT statement for non-inferiority trials.¹⁸

Methods

Patients

The study was approved by the ethics committee of the University of Ulm (Approval-No: 198/06) and registered at ClinicalTrials.gov (NCT01076894). The study group consisted of patients undergoing elective pulmonary surgery, including pneumonectomy, bilobectomy, lobectomy, segmentectomy, and wedge resection, via an antero-lateral muscle-sparing thoracotomy without chest-wall resection. Exclusion criteria were: age <18 yr; any contraindication to EDA, intercostal nerve block, or to the use of ropivacaine, morphine, metazolone, or diclofenac; inability to understand the pain scale or to perform a spirometry; and any type of chronic painful condition or current opioid use.

After written informed consent was obtained, the patients were randomly assigned to one of the two treatment groups by opening a closed numbered envelope produced by the Institute of Biometrics at the University of Ulm. The randomization was done by a block randomization using a self-developed validated programme, which is used as a standard tool in this institute. The randomization programme allows the printing of randomization envelopes on paper overprinted with numbers to aid code concealment.

Preoperative management

On the day before operation, the use of a numeric rating scale (NRS) graduated from 0 (no pain) to 10 (worst pain) was explained to the patient and baseline pain data were obtained.¹⁹ The patient-controlled analgesia pump device was also explained, Graseby 9300[®] (Graseby Medical Limited, Watford, UK) in the case of allocation to the intercostal group or Cadd Prizm Type 2 (Smiths Medical, Germany) in the case of allocation to the epidural group. Furthermore, all patients were instructed in the use of a hand-held spirometer (SP-200, Schiller AG, Baar, Switzerland) and preoperative baseline spirometric data collected.

Anaesthetic procedure

Epidural anaesthesia

Before the induction of general anaesthesia, a thoracic epidural catheter was placed at the level of T6–T8 and was advanced 5–7 cm into the epidural space. Then a 3 ml test dose of mepivacaine 1% was administered. Provided that there was no rapid onset of neuroaxial block suggesting subarachnoid delivery of the local anaesthetic, an additional ropivacaine 1% (8 ml) was administered. After 30 min, the sensory block was tested by pinprick. EDA was aimed at a sensory block level from T2 to T10. If the desired block level was not achieved, ropivacaine 1% (3 ml) was administered and after 30 min, the sensory block was re-evaluated. The patient was excluded from the study if the catheter could not be placed or the target sensory block level could not be achieved by the second administration of ropivacaine. Intraoperatively, administration of ropivacaine 1% (5 ml) was repeated every 60 min.

Intercostal nerve block

In the intercostal block (ICB) group, before chest closure, each ropivacaine 0.75% (4 ml) was injected by the surgeon under direct vision into the proximal intercostal space at the level of the thoracotomy and two spaces above and below, and also ropivacaine 0.75% (5 ml) at the thoracic drainage tube exits. Thus, a total of 30 ml ropivacaine 0.75% (225 mg) were administered.

General anaesthesia

Patients received oral benzodiazepine premedication with clorazepate dipotassium (20 mg) in the evening and midazolam (7.5 mg) 1 h before induction of anaesthesia. General anaesthesia was induced with propofol (2–3 mg kg⁻¹), fentanyl (2–4 µg kg⁻¹), and tracheal intubation with a left-sided double-lumen tube was facilitated by atracurium 0.5 mg kg⁻¹. A radial artery catheter was placed. Anaesthesia was maintained with desflurane, fentanyl, and remifentanyl as necessary. The tidal volume during one-lung ventilation was 6 ml kg⁻¹, the ventilatory frequency was 12–16 bpm, and PEEP was 5 cm H₂O. After induction of general anaesthesia, all patients received 1 g of metazolone (Novalgin[®]) i.v. and 100 mg of diclofenac (Voltaren[®]) rectally.

Postoperative pain management

In patients in the epidural group, patient-controlled epidural analgesia (PCEA) was initiated immediately after arrival in the recovery room. PCEA was achieved with a mixture of 0.2% ropivacaine and sufentanil (2 µg ml⁻¹) with 3 ml bolus doses permitted every 15 min without a continuous infusion. During observation in the recovery room, the lockout period of 15 min could be deactivated and boluses could be given by the nurse if necessary. Opioids other than sufentanil through the epidural catheter were not administered routinely during the study period. If epidural analgesia was judged to be inadequate, for example, in patients

with shoulder pain, rescue analgesia in the form of i.v. morphine was given in the recovery room.

In patients in the intercostal group on arrival in the recovery room, morphine PCA was started using 2 mg bolus, 15 min lockout period, and no background infusion. The lockout period could be deactivated and a bolus could be given by the nurse if necessary during observation in the recovery room.

The epidural catheter with the PCEA pump and the morphine PCA pump were maintained until the evening of the fourth postoperative day. Patients of both groups received diclofenac 75 mg 12 hourly, orally, and metamizole 1 g 6 hourly, i.v. or orally, during the first four postoperative days.

Data collection

Before operation, age, weight, height, and ASA classification, pain status (NRS at rest and on coughing) were assessed. Intraoperatively, type and duration of surgery, total dose of fentanyl and remifentanyl, and total volume of administered blood, colloids, and crystalloids were recorded. After operation, the following data were collected 1 h after arrival in the recovery room, before discharge from the recovery room, in the evening after operation (8:00 p.m.), and on each morning (8:00 a.m.) and evening (8:00 p.m.) during the first four postoperative days.

Pain intensity at rest and during coughing using the NRS score; intensity of coughing (five-point scale: 0, no cough; 1, slight cough; 2, cough; 3, productive cough; 4, violent cough); average and maximum pain intensity since the last questioning, sedation score (four-point score; 0, does not open eyes to verbal command; 1, sleeping, easy to arouse verbally; 2, drowsy; 3, alert); nausea or vomiting episodes; SpO₂; overall satisfaction with pain management (five-point score: 0, very dissatisfied; 1, dissatisfied; 2, indecisive; 3, happy; 4, very happy); and cumulative morphine and ropivacaine plus sufentanil consumption in the intercostal and epidural groups, respectively.

On discharge from hospital, the following data were recorded: length of stay on the intensive care unit (ICU), total length of hospital stay after surgery, and the occurrence of any postoperative complication.

Spirometric measurements

All tests were performed at bedside with the patient in a sitting or semirecumbent position by one of the two investigators (S.K. and E.B.). Inspiratory vital capacity (IVC), forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), and peak expiratory flow rate (PEFR) measured by the use of a hand-held spirometer (SP-200, Schiller AG, Baar, Switzerland). The spirometric measurements were performed the day before operation, in the evening after operation, and in the morning during the first four postoperative days (POD1–POD4).

Outcomes

The primary outcome variable was pain at rest on the first postoperative day.

Secondary outcome variables included pain scores at rest at the other time points, pain scores on coughing assessed in the recovery room, in the evening after operation, and twice daily during the first four postoperative days, and average and maximum pain scores 'since the last questioning'. A further secondary outcome variable was pulmonary function assessed by spirometric parameters IVC, FVC, FEV1, and PEFR in the evening after operation and in the morning during the first four postoperative days.

Other secondary outcomes considered included overall satisfaction with pain management, incidence of postoperative pruritus, nausea, or vomiting, and postoperative sedation. Additional secondary outcomes included postoperative complications, readmissions to the ICU, length of ICU stay, length of hospital stay, and in-hospital deaths.

Statistical analysis

The number of patients required in each group with pain at rest on the first postoperative day as the primary outcome variable was determined from a power analysis on the basis of non-inferiority hypothesis.²⁰ For non-inferiority of the intercostal nerve block vs thoracic EDA, a maximum difference of 0.5 (margin of non-inferiority) on the NRS scale was considered as acceptable. On the basis of previously published data,^{10 21} a standard deviation of 1.5 was assumed for NRS distribution. Under these conditions, 40–45 patients per group are required to reach a power of 74–94 % (one-sided hypothesis, α 2.5%). Thus, we decided to include at least 40 evaluable patients per group.

Because of the non-normal distribution, NRS scores were presented as median and 95% confidence interval of the median.^{22 23} Pulmonary function variables are presented as 'box plots'.

Analysis of the primary outcome variable, pain at rest on the first postoperative day, was performed according to a non-inferiority approach.¹⁸ The 95% confidence intervals of the median treatment difference in NRS scores were calculated using the 'Hodges–Lehman Estimator' as proposed by Altman and colleagues²⁴ and presented in relation to the predefined margin of inferiority and null effect.¹⁸

All secondary outcome variables were analysed in terms of an explorative data analysis. Differences between the two groups regarding intraoperative and postoperative outcome variables were analysed using the Mann–Whitney rank-sum test for continuous variables and Fisher's exact test for categorical variables. Also intergroup differences of NRS scores and pulmonary function variables were analysed by multiple use of the Mann–Whitney rank-sum test at the different time points in terms of an explorative data analysis. For all these analyses, a *P*-value of <0.05 was considered to be significant.

The statistical software used was SigmaStat for Windows version 3.0 (SPSS, Chicago, IL, USA) and for non-inferiority analysis SAS version 9.2 (SAS, Cary, NC, USA).

Results

Over a period of 21 months, from February 2007 to October 2008, 92 patients were randomly allocated to one of the two groups (Fig. 1). After exclusion of four patients (two patients in the epidural group because of failure to place the epidural catheter and two patients in the intercostal group because of thoracoscopic surgery and cancelled operation, respectively), 88 patients were considered for analysis. A further five patients were excluded from pain and pulmonary function analysis (for details, see Fig. 1). Thus, the pain and pulmonary function analyses were based on 41 patients in the epidural group and 42 patients in the intercostal group.

As seen in Table 1, patient characteristics were similar in both groups. Because of chance, more patients of the intercostal group ($n=6$) underwent pneumonectomy when

compared with the epidural group ($n=2$). One pneumonectomy patient of the intercostal group was mechanically ventilated more than 12 h, and thus excluded from the pain and pulmonary function analysis.

Duration of surgery did not differ between the groups. Intraoperatively, more opioids were administered in the intercostal group, whereas there was a trend to a greater fluid administration in the epidural group (Table 1). None of the patients suffered from any serious complications related to EDA, intercostal nerve block, or patient-controlled anaesthesia. Three patients of the epidural group required additional i.v. morphine in the recovery room. Two of these patients suffered from shoulder pain. Daily use of morphine and ropivacaine plus sufentanil in the intercostal and epidural groups, respectively, is given in Supplementary Table S1.

Overall, at rest, postoperative pain control was good for both the epidural and intercostal groups (Fig. 2A).

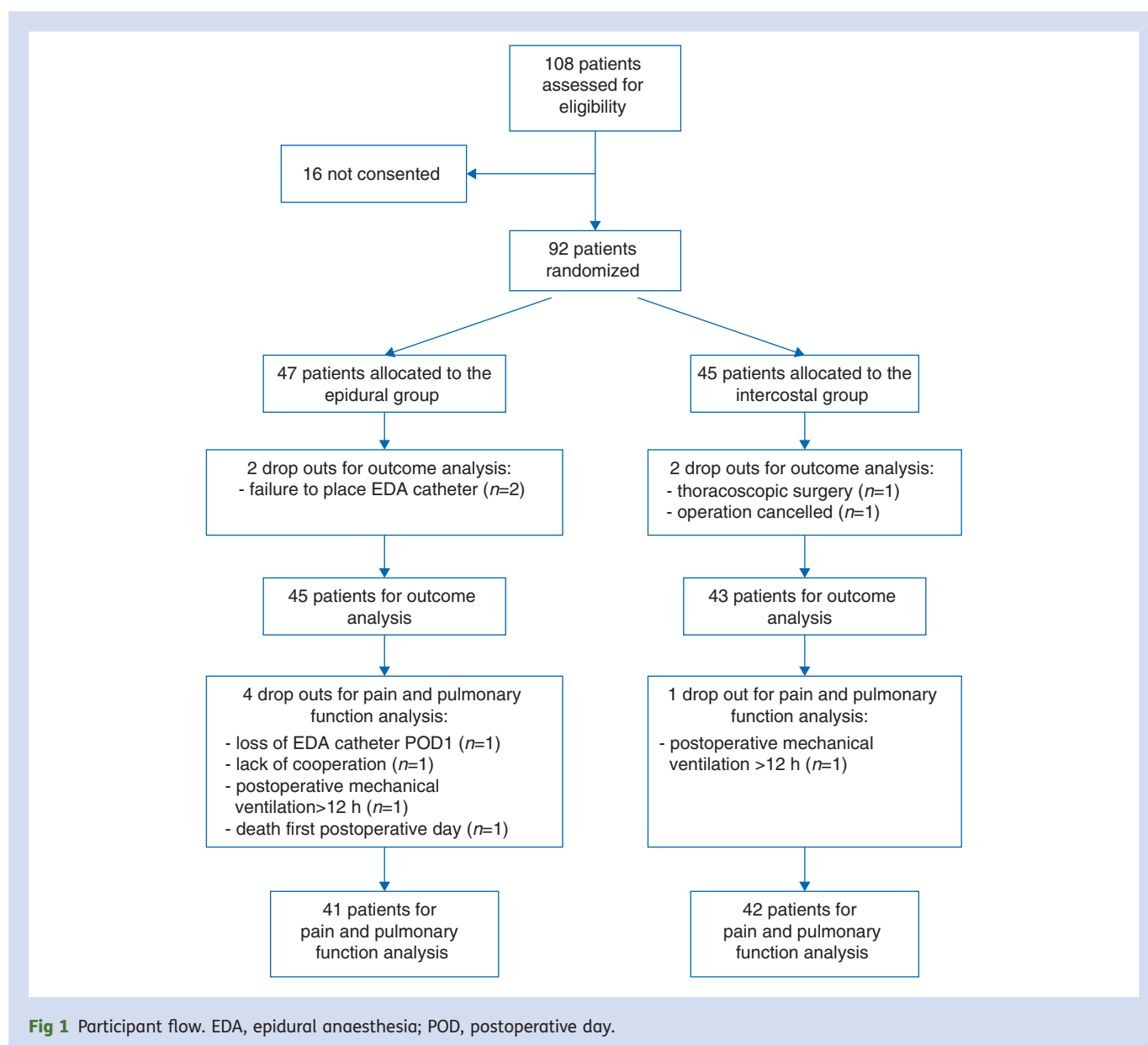


Table 1 Patient characteristics, type and duration of surgery, and anaesthetic requirements. Data given as median (range) or number of patients. ASA, American Society of Anesthesiologists. *Fluid therapy during surgery (crystalloid and colloid)

	Epidural group (n=45)	Intercostal group (n=43)	P-value
Sex (F/M)	12/33	9/34	—
Age (yr)	64 (24–74)	65 (28–87)	—
Height (cm)	174 (158–190)	170 (155–188)	—
Weight (kg)	75 (56–108)	76 (52–107)	—
ASA physical status (I/II/III/IV)	1/6/36/1	2/8/33/0	—
Pulmonary diagnosis (benign/malignant tumour)	6/39	8/35	—
Type of surgery			
Pneumonectomy	2	6	—
Bilobectomy	2	2	—
Lobectomy	17	16	—
Segmentectomy or wedge resection	24	19	—
Duration of surgery (min)	120 (60–390)	120 (65–230)	0.65
Total amount of fentanyl (mg)	0.5 (0.4–1.0)	1.1 (0.5–2.0)	0.001
Total amount of remifentanyl (mg)	0.8 (0.0–2.7)	1.5 (0.3–3.9)	0.003
Total amount of fluid use* (litre)	2.5 (1.5–6.0)	2.3 (1.0–4.0)	0.07

The 95% confidence interval of the median treatment differences regarding NRS scores at rest on the first postoperative day failed to demonstrate non-inferiority of the intercostal nerve block as shown in Figure 3.

Comparisons of the NRS values on coughing demonstrated significantly higher values in the intercostal group during the first and second postoperative days (Fig. 2b). Also regarding the ‘maximum pain experienced since the last questioning’, patients of the intercostal group reported significantly higher NRS values during the first and second postoperative days (Fig. 2c). Furthermore, the ‘average experienced pain since the last questioning’ was significantly lower in the epidural group during the second postoperative day (data not shown).

Episodes of nausea or vomiting were complained of most frequently in the evening after operation (32% epidural group vs 13% intercostal group, $P=0.06$) and in the evening of the first postoperative day (22% epidural group vs 29% intercostal group, $P=0.62$) without a significant difference between the groups (Table 2). A considerable number of patients suffered from pruritus with a trend to a more frequent occurrence in the epidural group. Most frequently, pruritus was observed in the evening of the second postoperative day (29% epidural group vs 17% intercostal group, $P=0.02$). The postoperative sedation score did not show a clinically important difference between the groups. Overall, patient

satisfaction with the pain therapy was satisfactory in both groups. However, there was a trend to higher satisfaction scores reported by the patients of the epidural group from the second to the fourth postoperative day (Table 2).

The time course of changes in the spirometric variables is shown in Figure 4. Overall, pulmonary function was better preserved in the epidural group. The epidural group demonstrated a significantly higher FVC at the first and second postoperative days, and a significantly higher FEV1 and PEF at the second postoperative day. As these results might be affected by the larger number of patients undergoing pneumonectomy in the intercostal group ($n=5$ in the intercostal group vs $n=2$ in the epidural group), all pulmonary function variables were recalculated after omitting pneumonectomy patients. This analysis demonstrated a trend to a better preserved pulmonary function in the epidural group, even if the differences were statistically not significant (Supplementary Table S2).

The incidence of any pulmonary complications (13/45 vs 11/43; $P=0.81$), median length of ICU stay (1 vs 1 days; $P=0.86$), median length of hospital stay of the surviving patients (13 vs 13 days; $P=0.88$), and in-hospital death rate (2/45 vs 2/43; $P=1.0$) did not differ between the epidural and the intercostal groups.

Discussion

The present study failed to confirm our hypothesis that a single intercostal nerve block with ropivacaine in combination with patient-controlled i.v. morphine is as effective as patient-controlled thoracic EDA with respect to postoperative pain control and pulmonary function after lateral thoracotomy.

Median treatment differences regarding pain scores at rest failed to demonstrate non-inferiority of the intercostal nerve block at the first postoperative day. During the first two postoperative days, patients of the intercostal group reported higher NRS scores on coughing and also with respect to the ‘maximum pain experienced since the last questioning’. Furthermore, pulmonary function was better preserved in the epidural group during the first and second postoperative days.

To our knowledge, previous data regarding the analgesic effects of the single intercostal nerve block in comparison with thoracic EDA are scarce and are based on five smaller studies.^{10 14–17} None of these studies included more than 15 patients in each group, and only two of them combined intercostal nerve block with postoperative patient-controlled opioid administration.^{10 14} Perttunen and colleagues¹⁴ reported slight advantages of the ICB immediately after operation and equivalent analgesic effects during the following 48 h. In contrast, Concha and colleagues¹⁰ observed slightly higher pain scores in the intercostal group, but the authors regarded the difference as clinically not significant.

On the basis of data reported by Perttunen and colleagues,¹⁴ it could be speculated that intercostal nerve block may induce analgesic effects of longer duration of

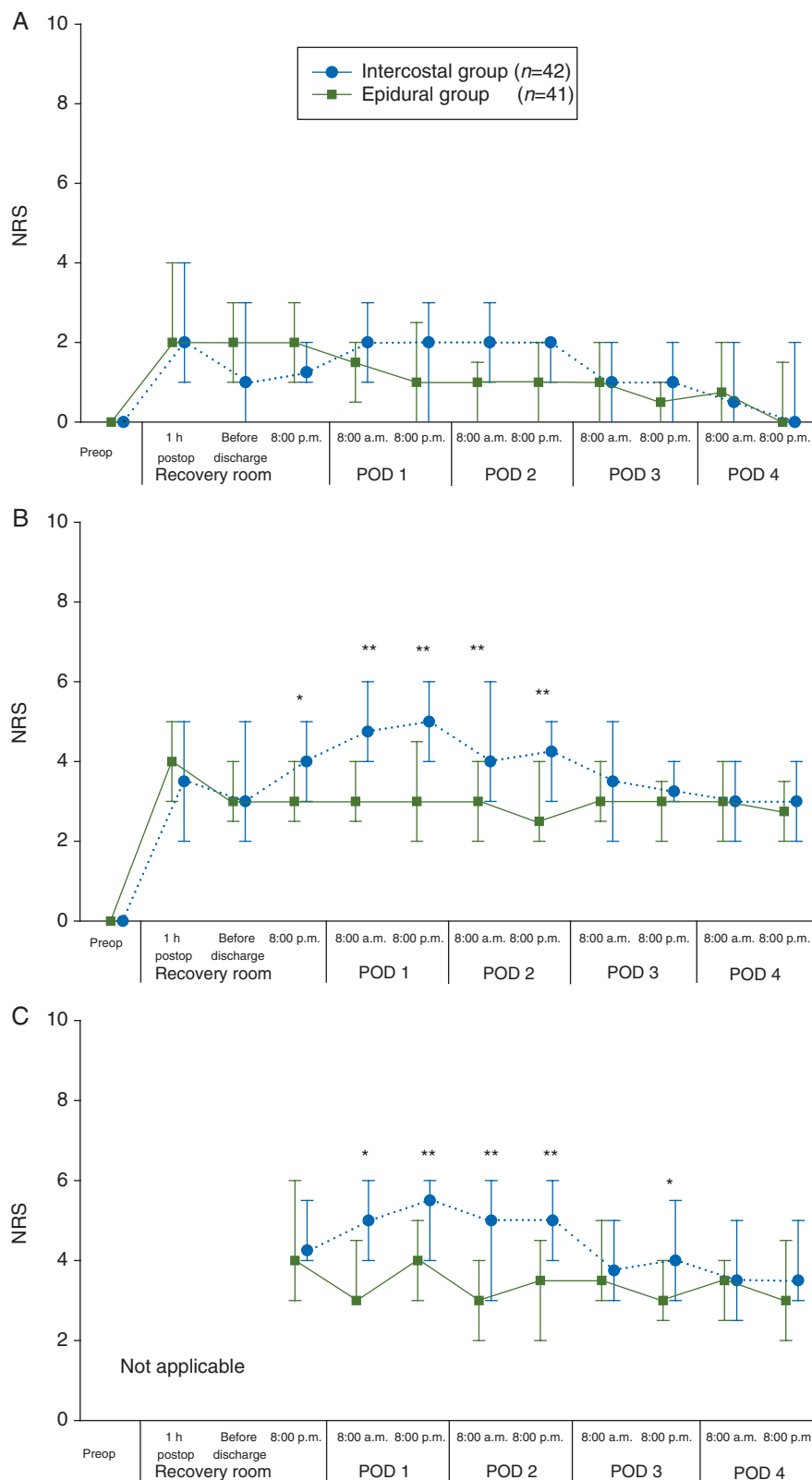


Fig 2 Pain course at rest (A), on coughing (B), and ‘maximum pain experienced since last questioning’ (C). Data given as median and 95% confidential interval of the median. * $P < 0.05$; ** $P < 0.01$: comparison between the epidural and intercostal groups (Mann–Whitney rank sum test). NRS, numeric rating scale; POD1, POD2, POD3, and POD 4, first, second, third, and fourth postoperative day.

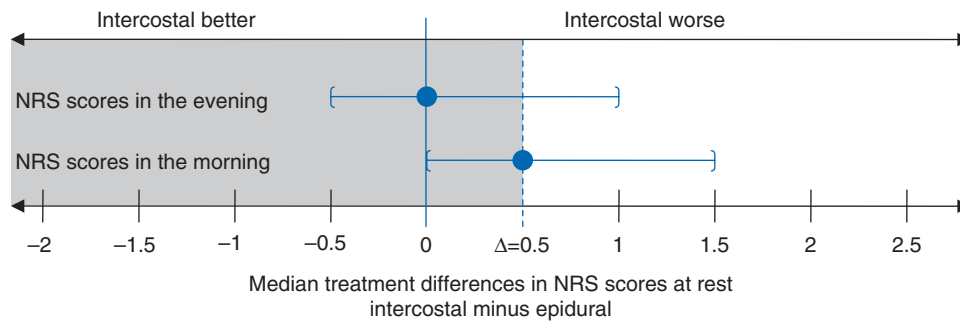


Fig 3 Median treatment differences for NRS scores at rest on the first postoperative day. Error bars indicate two-sided 95% confidence intervals. Δ , margin of non-inferiority. Non-tinted area indicates zone of inferiority. NRS, numeric rating scale.

Table 2 Nausea or vomiting, pruritus, sedation scores, and overall patient satisfaction. Data given as number (%) or median (95% confidential interval of the median). *P*-value, comparison between the epidural and intercostal groups. POD1, POD2, POD3, and POD4: first, second, third, and fourth postoperative day

Epidural group (n=41)	Day of operation, recovery room			POD1		POD2		POD3		POD4	
	1 h	Before discharge	8:00 p.m.	8:00 a.m.	8:00 p.m.	8:00 a.m.	8:00 p.m.	8:00 a.m.	8:00 p.m.	8:00 a.m.	8:00 p.m.
Nausea or vomiting, n (%)											
Epidural group	0 (0)	1 (3)	13 (32)	9 (22)	9 (22)	2 (5)	0 (0)	1 (2)	3 (8)	4 (10)	2 (5)
Intercostal group	1 (3)	0 (0)	5 (13)	9 (21)	12 (29)	5 (12)	5 (12)	1 (3)	5 (13)	2 (5)	3 (8)
<i>P</i> -value	0.46	0.49	0.06	1.00	0.62	0.43	0.06	1.00	0.71	0.68	1.00
Pruritus, n (%)											
Epidural group	1 (2)	1 (3)	4 (10)	8 (20)	11 (27)	9 (22)	12 (29)	3 (7)	5 (13)	5 (13)	3 (7)
Intercostal group	2 (6)	1 (3)	5 (13)	2 (5)	6 (14)	3 (7)	7 (17)	4 (10)	7 (18)	4 (10)	3 (8)
<i>P</i> -value	0.59	1.00	0.74	<0.05	0.18	0.07	0.20	0.71	0.76	0.76	1.00
Sedation score (0–3)											
Epidural group	3 (3–3)	3 (3–3)	3 (3–3)	3 (3–3)	3 (3–3)	3 (3–3)	3 (3–3)	3 (3–3)	3 (3–3)	3 (3–3)	3 (3–3)
Intercostal group	2.5 (2–3)	3 (3–3)	3 (2–3)	3 (3–3)	3 (3–3)	3 (3–3)	3 (3–3)	3 (3–3)	3 (3–3)	3 (3–3)	3 (3–3)
<i>P</i> -value	0.13	0.80	0.13	0.16	0.30	0.90	0.58	1.00	0.57	0.85	0.56
Patient satisfaction [0–4]											
Epidural group	–	–	3 (3–3)	–	3 (3–4)	–	4 (3–4)	–	3 (3–4)	–	3.5 (3–4)
Intercostal group	–	–	3 (3–3)	–	3 (3–3)	–	3 (3–3)	–	3 (3–3)	–	3 (3–3)
<i>P</i> -value	–	–	0.61	–	0.21	–	0.14	–	0.04	–	0.06

action than expected due to the pharmacokinetic of the local anaesthetic. In the present study, pain scores in the recovery room did not differ between both groups. However, already on the evening after operation, patients in the intercostal group reported higher pain scores on coughing when compared with the epidural group. Thus, the present data do not provide any evidence that the intercostal nerve block outlasts the expected duration of action of the local anaesthetic. This finding is in agreement with other studies that have investigated the effects of a single intercostal nerve block.^{11 13 15 25} In contrast to ICB, there is some evidence that a before operation paravertebral block may produce longer-acting analgesic effects due to a pre-emptive

analgesic effect. This potential of paravertebral block has been described in the context of breast surgery^{26 27} and thoracic surgery^{28 29} and it has been speculated that one reason for this effect of paravertebral block might be that, in contrast to the ICB, it completely blocks transmission within the sympathetic chain.³⁰

It has been hypothesized that due to respiratory motor block, thoracic EDA with local anaesthetics may impair pulmonary function. Sundberg and colleagues³¹ reported a reduction in IVC, but not FEV1, in volunteer patients undergoing high thoracic EDA with bupivacaine 0.5%. Moreover, in patients with severe obstructive pulmonary disease, thoracic EDA with ropivacaine 0.75% has been shown to slightly

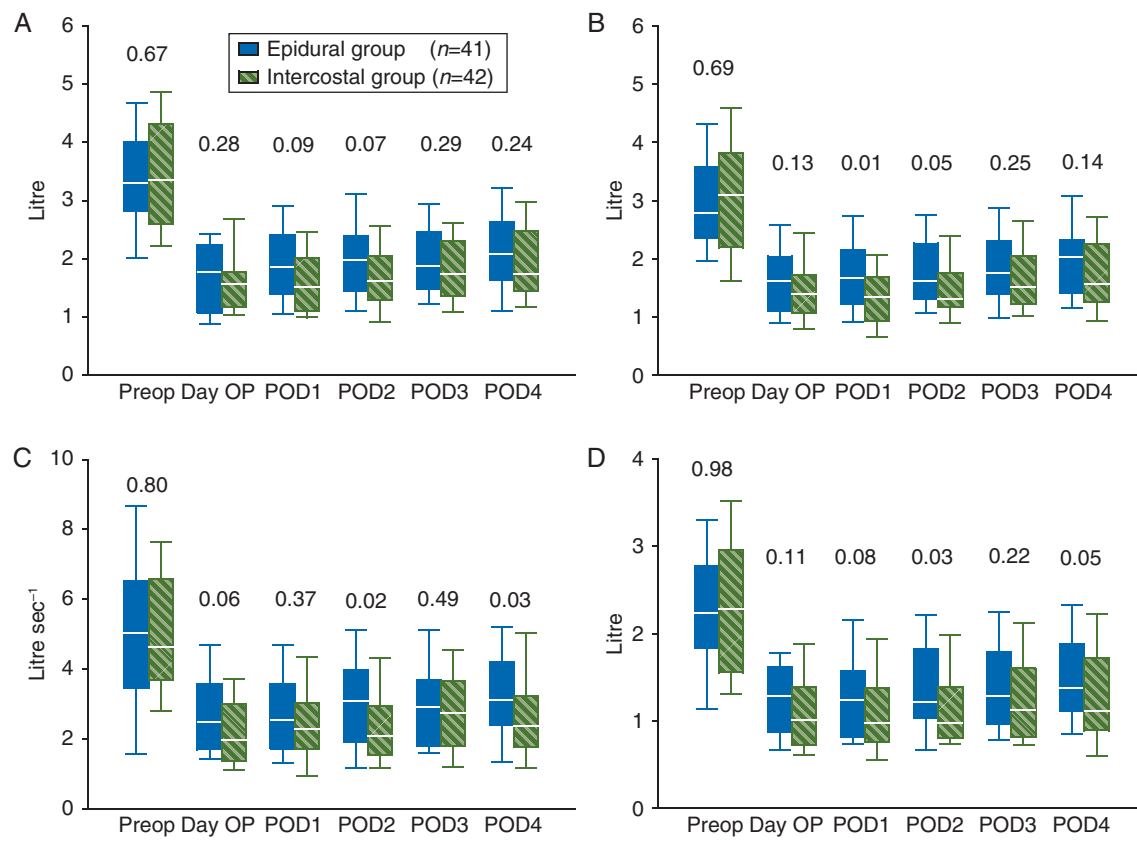


Fig 4 Time course of pulmonary function: IVC (A), FVC (B), PEFR (C), and FEV1 (D). The median, 5% percentile, 95% percentile, and inter-quartile range (box) are shown. *P*-value, comparison between the epidural and intercostal groups (Mann–Whitney rank-sum test). IVC, inspiratory vital capacity; FVC, forced vital capacity; PEFR, peak expiratory flow rate; FEV1, forced expiratory volume 1; POD1, POD2, POD3, and POD 4, first, second, third, and fourth postoperative day.

reduce FVC and FEV1.³² However, in the present study using ropivacaine 0.2% with sufentanil 2%, we observed better preserved spirometric respiratory function variables in the epidural group, even if the difference between both groups was not significant with respect to the IVC. With this combination of local anaesthetic and opioids, the positive analgesic effects of EDA appear to outweigh potential negative effects on respiratory muscles. This finding is in agreement with results reported by Bauer and colleagues³³ who investigated postoperative respiratory function under thoracic EDA in comparison with patient-controlled i.v. morphine in patients after lobectomy.

With respect to pulmonary complications, length of hospital stay, or in-hospital mortality, we did not find any differences between the groups. However, these were not the primary endpoints of this study and this study is underpowered to detect potential differences between the treatment groups.

The data analysis was not performed according to an intention-to-treat analysis based on all randomized patients. However, for non-inferiority trials, it is recommended that the analysis should include only those patients who received

the intended treatment in order to avoid an increase in type I error risk.¹⁸ As in many previous randomized controlled trials that have investigated the effects of EDA,^{7 34 35} in the present study, treatment allocation was not concealed, which may have biased the results in either direction. A double-masked protocol would require placement of an epidural catheter and injection of a placebo in one patient group. In our opinion, this is difficult to justify. In order to minimize the possible bias, the investigators (E.B. and S.K.) of the pain scores and spirometric measurements were not informed about the hypothesis of this study.

In conclusion, we have found that single intercostal nerve block in combination with patient-controlled i.v. morphine is not as effective as patient-controlled thoracic EDA regarding postoperative pain control and pulmonary function after lung surgery via lateral thoracotomy. However, the clinical impact of this finding is not straightforward. Although we were not able to demonstrate non-inferiority of the intercostal nerve block, both analgesic regimes provided an excellent pain control at rest. Furthermore, the benefits regarding pain control and pulmonary function should be weighed against the potential risks of EDA.^{3–5} On the other hand, the

observed superiority of EDA with respect to pain control and pulmonary function may have implications on clinically important outcomes, such as pulmonary complication rates and perioperative mortality. This might be true in particular for patients with pre-existing severe pulmonary disease. Further larger trials are required to answer these issues.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Acknowledgement

We thank Dr Christina Ring, Institute of Biometrics, for her assistance in statistical analysis.

Conflict of interest

None declared.

Funding

This work was supported solely from departmental sources. None of the authors has been funded by any foundation or other non-governmental source which has received funding from any organization with a real or potential interest in the subject matter, materials, equipment, or devices discussed.

References

- Joshi GP, Bonnet F, Shah R, et al. A systematic review of randomized trials evaluating regional techniques for postthoracotomy analgesia. *Anesth Analg* 2008; **107**: 1026–40
- Gottschalk A, Cohen SP, Yang S, Ochroch EA. Preventing and treating pain after thoracic surgery. *Anesthesiology* 2006; **104**: 594–600
- Moen V, Dahlgren N, Irestedt L. Severe neurological complications after central neuraxial blockades in Sweden 1990–1999. *Anesthesiology* 2004; **101**: 950–9
- Brull R, McCartney CJ, Chan VW, El Beheiry H. Neurological complications after regional anesthesia: contemporary estimates of risk. *Anesth Analg* 2007; **104**: 965–74
- Cook TM, Counsell D, Wildsmith JA. Major complications of central neuraxial block: report on the Third National Audit Project of the Royal College of Anaesthetists. *Br J Anaesth* 2009; **102**: 179–90
- Davies RG, Myles PS, Graham JM. A comparison of the analgesic efficacy and side-effects of paravertebral vs epidural blockade for thoracotomy—a systematic review and meta-analysis of randomized trials. *Br J Anaesth* 2006; **96**: 418–26
- Richardson J, Sabanathan S, Jones J, Shah RD, Cheema S, Mearns AJ. A prospective, randomized comparison of preoperative and continuous balanced epidural or paravertebral bupivacaine on post-thoracotomy pain, pulmonary function and stress responses. *Br J Anaesth* 1999; **83**: 387–92
- Detterbeck FC. Efficacy of methods of intercostal nerve blockade for pain relief after thoracotomy. *Ann Thorac Surg* 2005; **80**: 1550–9
- Richardson J, Lonnqvist PA. Thoracic paravertebral block. *Br J Anaesth* 1998; **81**: 230–8
- Concha M, Dagnino J, Cariaga M, Aguilera J, Aparicio R, Guerrero M. Analgesia after thoracotomy: epidural fentanyl/bupivacaine compared with intercostal nerve block plus intravenous morphine. *J Cardiothorac Vasc Anesth* 2004; **18**: 322–6
- Kaplan JA, Miller ED Jr, Gallagher EG Jr. Postoperative analgesia for thoracotomy patients. *Anesth Analg* 1975; **54**: 773–7
- Takamori S, Yoshida S, Hayashi A, Matsuo T, Mitsuoka M, Shirouzu K. Intraoperative intercostal nerve blockade for post-thoracotomy pain. *Ann Thorac Surg* 2002; **74**: 338–41
- Liu M, Rock P, Grass JA, et al. Double-blind randomized evaluation of intercostal nerve blocks as an adjuvant to subarachnoid administered morphine for post-thoracotomy analgesia. *Reg Anesth* 1995; **20**: 418–25
- Perttunen K, Nilsson E, Heinonen J, Hirvisalo EL, Salo JA, Kalso E. Extradural, paravertebral and intercostal nerve blocks for post-thoracotomy pain. *Br J Anaesth* 1995; **75**: 541–7
- Wurnig PN, Lackner H, Teiner C, et al. Is intercostal block for pain management in thoracic surgery more successful than epidural anaesthesia? *Eur J Cardiothorac Surg* 2002; **21**: 1115–9
- Asantila R, Rosenberg PH, Scheinin B. Comparison of different methods of postoperative analgesia after thoracotomy. *Acta Anaesthesiol Scand* 1986; **30**: 421–5
- Scheinin B, Scheinin M, Asantila R, Lindberg R, Viinamaki O. Sympatho-adrenal and pituitary hormone responses during and immediately after thoracic surgery—modulation by four different pain treatments. *Acta Anaesthesiol Scand* 1987; **31**: 762–7
- Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJ. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. *J Am Med Assoc* 2006; **295**: 1152–60
- Joos E, Peretz A, Beguin S, Famaey JP. Reliability and reproducibility of visual analogue scale and numeric rating scale for therapeutic evaluation of pain in rheumatic patients. *J Rheumatol* 1991; **18**: 1269–70
- D'Agostino RB Sr, Massaro JM, Sullivan LM. Non-inferiority trials: design concepts and issues—the encounters of academic consultants in statistics. *Stat Med* 2003; **22**: 169–86
- Debrececi G, Molnar Z, Szelig L, Molnar TF. Continuous epidural or intercostal analgesia following thoracotomy: a prospective randomized double-blind clinical trial. *Acta Anaesthesiol Scand* 2003; **47**: 1091–5
- Mantha S, Thisted R, Foss J, Ellis JE, Roizen MF. A proposal to use confidence intervals for visual analog scale data for pain measurement to determine clinical significance. *Anesth Analg* 1993; **77**: 1041–7
- Braitman LE. Confidence intervals assess both clinical significance and statistical significance. *Ann Intern Med* 1991; **114**: 515–7
- Altman D, Machin D, Bryant T, Gardner M. *Statistics with Confidence*, 2nd Edn. London: BMJ Books, 2000
- Woltering EA, Flye MW, Huntley S, Kapp P, Dwyer A, McLees B. Evaluation of bupivacaine nerve blocks in the modification of pain and pulmonary function changes after thoracotomy. *Ann Thorac Surg* 1980; **30**: 122–7
- Weltz CR, Greengrass RA, Lyerly HK. Ambulatory surgical management of breast carcinoma using paravertebral block. *Ann Surg* 1995; **222**: 19–26
- Naja MZ, Ziade MF, Lonnqvist PA. Nerve-stimulator guided paravertebral blockade vs. general anaesthesia for breast surgery: a prospective randomized trial. *Eur J Anaesthesiol* 2003; **20**: 897–903
- Vogt A, Stieger DS, Theurillat C, Curatolo M. Single-injection thoracic paravertebral block for postoperative pain treatment after thoracoscopic surgery. *Br J Anaesth* 2005; **95**: 816–21

- 29 Richardson J, Sabanathan S, Mearns AJ, Evans CS, Bembridge J, Fairbrass M. Efficacy of pre-emptive analgesia and continuous extrapleural intercostal nerve block on post-thoracotomy pain and pulmonary mechanics. *J Cardiovasc Surg (Torino)* 1994; **35**: 219–28
- 30 Lonnqvist PA. Pre-emptive analgesia with thoracic paravertebral blockade? *Br J Anaesth* 2005; **95**: 727–8
- 31 Sundberg A, Wattwil M, Arvill A. Respiratory effects of high thoracic epidural anaesthesia. *Acta Anaesthesiol Scand* 1986; **30**: 215–7
- 32 Groeben H, Schafer B, Pavlakovic G, Silvanus MT, Peters J. Lung function under high thoracic segmental epidural anesthesia with ropivacaine or bupivacaine in patients with severe obstructive pulmonary disease undergoing breast surgery. *Anesthesiology* 2002; **96**: 536–41
- 33 Bauer C, Hentz JG, Ducrocq X, et al. Lung function after lobectomy: a randomized, double-blinded trial comparing thoracic epidural ropivacaine/sufentanil and intravenous morphine for patient-controlled analgesia. *Anesth Analg* 2007; **105**: 238–44
- 34 Rigg JR, Jamrozik K, Myles PS, et al. Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial. *Lancet* 2002; **359**: 1276–82
- 35 Park WY, Thompson JS, Lee KK. Effect of epidural anesthesia and analgesia on perioperative outcome: a randomized, controlled Veterans Affairs cooperative study. *Ann Surg* 2001; **234**: 560–9