Original Article

Comparison of Thoracic Epidural and Intravenous Analgesia from the Perspective of Recovery of Respiratory Function in the Early Post-Thoracotomy Period in Lung Cancer Surgery

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Abstract

OBJECTIVE: Thoracic epidural analgesia (TEA) reduces pulmonary complications after thoracotomy. Hypothetically, this advantage is partially because of the preserved pulmonary function, which is achieved by the reduction of postoperative pain and immobility. This study aimed to compare the principal methods of analgesia through early postoperative spirometric performance and gas exchange parameters after elective lung cancer surgery. TEA or intravenous analgesia (IVA) involving pethidine was used as the principal method in our sample population.

MATERIAL AND METHODS: A total of 62 patients operated via the posterolateral thoracotomy approach were enrolled. Postoperative analgesia was secured using multimodal analgesia with either TEA with 0.1% bupivacaine or IVA. Pain perception was assessed with the visual analog scale (VAS) while at rest and on coughing. Arterial blood samples were collected at 1, 24, and 72 hours postoperatively. Preoperative and third postoperative day spirometric measurements were recorded.

RESULTS: There were no significant differences among the groups in terms of demographic characteristics, properties of surgical technique, and disease-associated conditions. VAS scores of the TEA group were lower at the 72-hour follow-up, but a considerable fraction of these differences did not reach statistical significance. Reduction in the forced expiratory volume in the first second and forced vital capacities was more prominent in the IVA group on the third postoperative day, but these were not statistically significant either. Oxygenation parameters favored TEA but remained comparable. Finally, the pH values were significantly lower in the IVA group at 1 and 72 hours postoperatively (p=0.008 and p=0.02, respectively).

CONCLUSION: We believe that TEA is advantageous over IVA with alteration of respiratory volumes during the early postoperative period.

KEYWORDS: Blood gas analysis, epidural analgesia, opioid analgesics, respiratory function tests, thoracotomy

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INTRODUCTION

Postoperative pain in lung cancer surgery is a well-established determinant of occurrence of respiratory complications. Impaired chest wall integrity, rib fractures, and intercostal neural damage lead to the alteration of the functional ventilatory capacity, and thus set the grounds for adverse early postoperative events [1-3]. Considering the fact that conventional systemic analgesia might not provide adequate pain relief or that considerably high doses are required to achieve that goal, regional analgesia techniques are a safe and effective option that could be used solo or as a complementary method [1, 4, 5]. Thoracic epidural analgesia (TEA) is accepted as the gold standard method for this purpose and plays an important role in enhanced recovery after surgery protocols [1, 2, 4-6].

Moreover, when TEA and conventional analgesia were compared, the former was shown to be superior in preserving cardiopulmonary functions, reducing stress response, facilitating the recovery of gastrointestinal motility, and enhancing immune modulation [5, 7, 8].

This study aimed to assess whether TEA provided additional benefit over the conventional multimodal parenteral analgesia protocol of our referral thorax center for alterations in blood gas analysis parameters and the recovery of functional capacity in the early postoperative period.

MATERIAL AND METHODS

Study Design and Patient Selection

This study was conducted at a tertiary referral center for thoracic surgery. A total of 62 patients with lung cancer (between the ages 18 and 75; American Society of Anesthesiologists [ASA] Class I to III) who underwent an elective thoracic surgical procedure with posterolateral thoracotomy were enrolled. The procedures were performed by the same surgical team. The sample size was determined by estimating the forced expiratory volume in the first second (FEV1) or forced vital capacity (FVC) change of 0.7±0.4 L. Power analysis indicated that 56 patients were needed for 80% power with a type I error of 5%. The study was approved by the local ethics committee and was performed as per global ethical standards. Written informed consent was obtained from all the participants.

The criteria for exclusion from the study were as follows:

- Age <18 years or >5 years,
- Significant psychiatric problems,
- Severe auditory deficit,
- Drug abuse,
- Cardiovascular system disorders with notable deterioration in functional capacity,
- Severe respiratory depression identified as a reduction of more than 50% of the predicted value of FVC,
- Refusal to give consent,
- Contraindication for epidural catheter insertion,
- Failure to spare serratus anterior muscle,
- Partial chest wall resection, and
- Failure of extubation before transfer to critical care unit.

TEA or pethidine-based intravenous analgesia (IVA) was selected as the pivotal component of multimodal analgesia. The patients were grouped according to the method of choice, which was at the anesthesiologist's discretion.

Features of Anesthetic Technique and Intraoperative Analgesia

TEA was performed before induction of anesthesia. The puncture of the epidural space was performed with an 18G Tuohy needle (Pajunk, Geisingen, Germany) by loss of resistance method at the level of T3-T7. After the insertion of the catheter, 2 mL of 2% lidocaine HCl was administered for confirmation. A 10 mL bolus dose of 0.1% bupivacaine was

injected thereafter. During the operation and for 24 hours postoperatively, 0.1% bupivacaine (0.1 mL/kg/hour) was given through the catheter.

Induction of anesthesia was achieved by midazolam (0.04 mg/kg), propofol (2 mg/kg) and fentanyl (1 mcg/kg) in both the groups. Cisatracurium besylate (0.2 mg/kg) was used for neuromuscular blockade. A double-lumen tracheal tube was then inserted, and proper positioning was verified with a fiberoptic bronchoscope. The ventilation mode was selected for pressure control. In the operating room, arterial and central venous pressures, heart rhythm, gas exchange parameters, and urine output were closely monitored. Body temperature was maintained over 36°C with the help of a warming system. In the TEA group, 0.5–2 MAC sevoflurane, which also exhibits analgesic properties, was additionally used. In the IVA group, remifentanil (0.1-0.2 mcg/kg/min) and sevoflurane were used in combination for analgesia. If the arterial pressure exceeded a value of 20% or more of the baseline recordings, 1 mcg/kg fentanyl was administered. Every 1 hour, an additional dose of cisatracurium besylate (0.25 mg/kg) was administered to ensure complete myorelaxation.

The intercostal blockade was invariably applied by the surgical team before closing the wound. Bupivacaine 0.25% (4 mL) was injected at the region of incision and 2 adjacent intercostal sites. According to the strategy of multimodal analgesia, morphine sulfate (0.1 mg/kg), tramadol (100 mg), paracetamol (15 mg/kg, 1000 mg maximum), and tenoxicam (20 mg) were given intravenously before the closure of the wound. For lobectomy or bilobectomy, anterior 28 Ch and posterior 32 Ch drainage tubes were inserted. For pneumectomy, only the latter was placed. Spontaneous ventilation and verbal response were assessed after the reversal of the neuromuscular blockade. The patients were then transferred to the critical care unit.

Perioperative data, including procedure time, type of operation (lobectomy or pneumectomy), duration of tube drainage, and occurrence of surgery-related complications, were recorded. Procedure time was defined as the time interval between the induction of anesthesia and extubation of the patient.

Assessment of Pain

Visual analog score (VAS), with a scale between 0 and 10, was used to define the severity of pain [3]. The VAS system was explained to the patient on the day before the operation. Thoracic pain was assessed by a healthcare professional (who was blinded to the study) at the 1st, 6th, and 12th hours of the postoperative period. The VAS values were noted both while at rest (VAS-R) and while coughing (VAS-C).

Spirometric Tests and Arterial Blood Gas Analyses

FEV1 and FVC of the patients were measured and recorded, both preoperatively and on the third postoperative day. FEV1/FVC ratio was also calculated.

Blood samples for arterial blood gas analyses were collected at 1 and 24 hours after the termination of the procedure during nasal inhalation of oxygen (2 mL/min). At 72 hours, the

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MAIN POINTS

- Thoracic epidural and intravenous analgesia were compared by means of early recovery of respiratory function.
- Alteration of the spirometric parameters was statistically comparable among treatment arms.
- There was a tendency trend towardsfor lower reduction of FEV1 and FVC on the third postoperative day in the TEA group.
- The mean pH value of the patients who received total intravenous analgesia was significantly lower at the 1st and 72nd postoperative hours.

last sample was drawn without oxygen support. PO$_2$, PCO$_2$, SaO$_2$, pH values, and bicarbonate levels were noted.
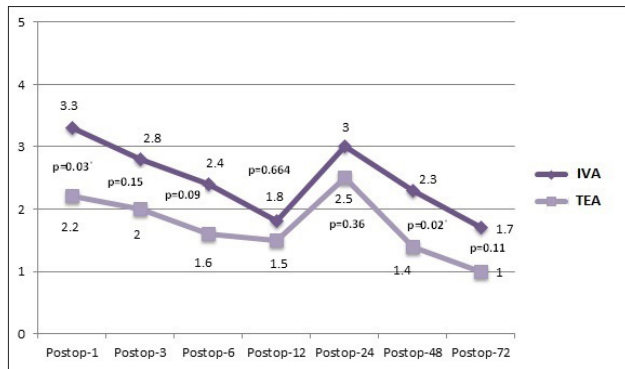

Figure 1. Stacked line charts demonstrating mean visual analog scale cores of patients at rest. The horizontal axis represents time in hours. ($^\times$) indicates significant p values. IVA, intravenous analgesia; TEA, thoracicepidural analgesia
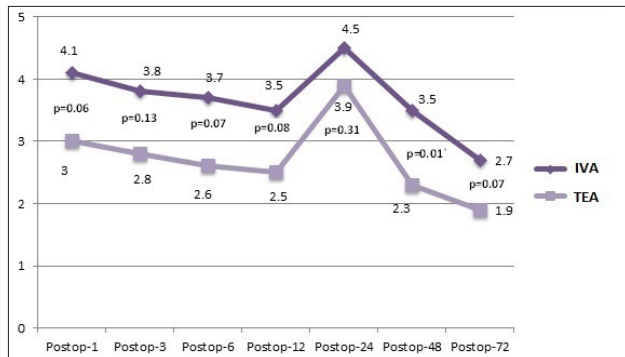

Figure 2. Stacked line charts demonstrating mean visual analog scale scores of patients during coughing. The horizontal axis represents time in hours. ($^\times$) indicates significant p values. IVA, intravenous analgesia; TEA, thoracicepidural analgesia

Postoperative Analgesia Management
In the TEA group, bupivacaine was administered through the epidural catheter for the first 24 hours as described earlier. In the IVA group, pethidine infusion (0.25 mg/kg/hour) was used instead. Intravenous paracetamol (1000 mg, every 6 hours) and tenoxicam (20 mg, every 12 hours) were additionally used in both groups.

Respiratory physiotherapy was initiated 24 hours postoperatively using incentive spirometry, assisted cough, and staged mobilization.

A VAS score of 3 or lower was defined as indicative of tolerable pain. If the VAS-R or VAS-C was >7, the patient was excluded from the study and the treatment strategy was modified. For scores between 4 and 7, an additional bolus dose of 10 mL of 0.1% bupivacaine was given, and the infusion rate was increased by 2 mL/hour in the TEA group. In the IVA group, an additional bolus dose of 0.5 mg/kg pethidine was given, and the infusion rate was increased by 0.35 mg/kg/hour.

Statistical Analysis
Continuous variables were tested for normal distribution with the Kolmogorov-Smirnov test and confirmed by histograms. They were expressed as mean±standard deviation or median (maximum-minimum). Categorical variables were described as percentages (number of cases). The unpaired t and Mann-Whitney U tests were used to discriminate the continuous parameters with and without normal distribution, respectively. Pearson, Chi-squared, and Fisher exact tests were used for comparing the categorical variables. A p-value below 0.05 was considered statistically significant. The Statistical Package for the Social Sciences version 22.0 software (IBM SPSS Corp.; Armonk, NY, USA) was used to perform these analyses.
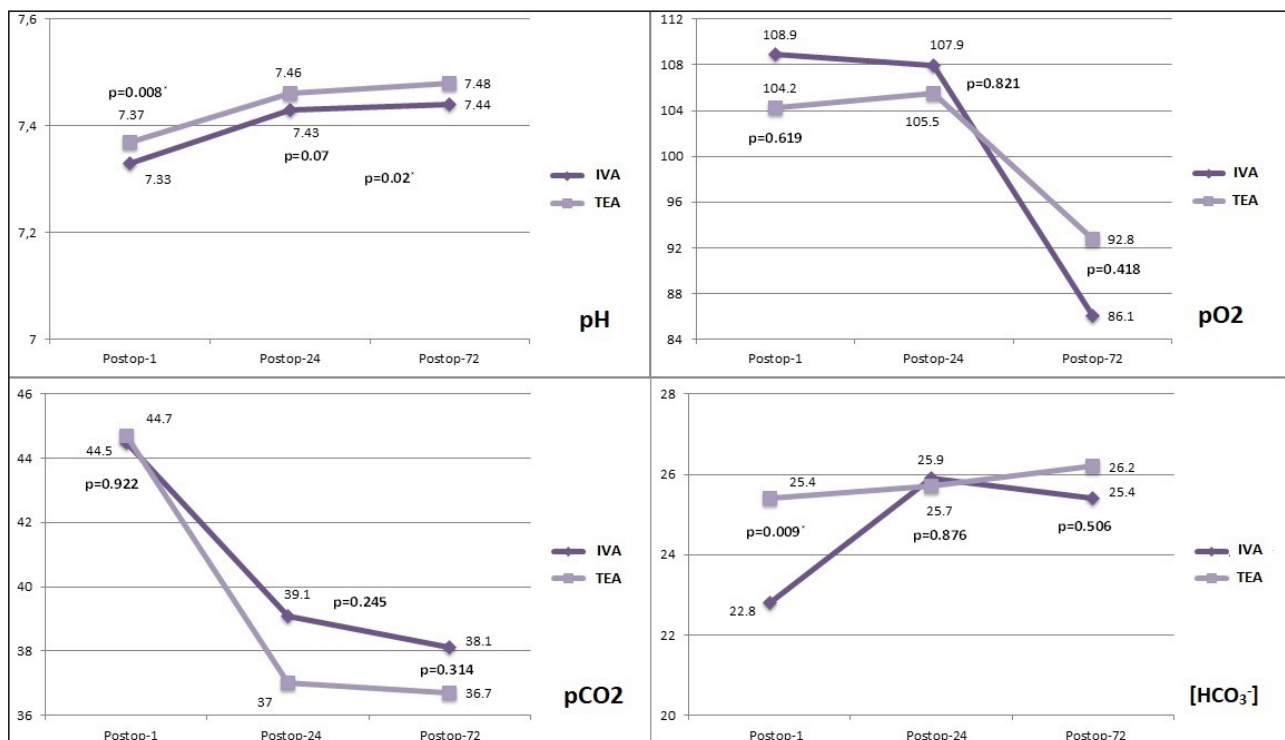

Figure 3. Stacked line charts demonstrating blood gas analysis results of patients. The horizontal axis represents time in hours. ($^\times$) indicates significant p values. IVA, intravenous analgesia; TEA, thoracicepidural analgesia

Table 1. Demographic, preoperative spirometric, and operation-related characteristics of sample population

	IVA (n=35)	TEA (n=27)	p
Sex			
Male, n (%)	33 (94.3)	24 (88.9)	
Female, n (%)	2 (5.7)	3 (11.1)	0.439
Age, years (mean±SD)	57.8±5.5	55.9±6.2	0.782
BMI, kg/m2 (mean±SD)	25.9±4.6	25.5±3.2	0.731
Smoking history, package/ years (mean±SD)	41.8±33.5	37.7±29.5	0.652
ASA score			
I, n (%)	2 (5.7)	1 (3.7)	
II, n (%)	19 (54.3)	14 (51.9)	
III, n (%)	14 (40.0)	12 (44.4)	0.898
Preoperative FEV1			
Liters±SD	2.35±0.66	2.08±0.62	0.103
% of predicted value±SD	80.0±20.0	74.0±21.7	0.264
Preoperative FVC			
Liters±SD	3.10±0.84	2.75±0.71	0.08
% of predicted value±SD	84.5±14.7	78.4±18.7	0.194
Preoperative FEV1/FVC %±SD	76.4±10.9	77.9±11.8	0.66
Type of operation			
Lobectomy, n (%)	27 (77.1)	18 (66.7)	
Pneumectomy, n (%)	8 (22.9)	9 (33.3)	0.359
Procedure time, minutes (mean±SD)	325.1±68.4	323.1±83.7	0.918
Duration of tube drainage, days (mean±SD)	5.2±2.7	4.5±2.3	0.285
Procedure-related complication, n (%)	2 (5.7)	3 (11.1)	0.645

BMI: body mass index; FEV1: forced expiratory volume in the first second; FVC: forced vital capacity; IVA: intravenous analgesia; TEA: thoracic epidural analgesia; SD: standard deviation; ASA: American Society of Anesthesiologists

Table 2. Postoperative spirometric measurements and amount of reduction compared with preoperative measurements

	IVA (n=35)	TEA (n=27)	p
Postoperative FEV1			
Liters±SD	1.58±0.49	1.38±0.45	0.19
% of predicted value±SD	53.3±12.7	48.7±13.4	0.24
Postoperative FVC			
Liters±SD	1.98±0.54	1.71±0.44	0.09
% of predicted value±SD	54.7±11.5	48.9±14.2	0.13
Postoperative FEV1/FVC			
%±SD	77.6±12.1	80.4±12.3	0.66
Reduction in FEV1			
Liters±SD	0.75±0.43	0.63±0.54	0.39
% of predicted value±SD	28.1±12.6	24.9±23.4	0.54
Reduction in FVC			
Liters±SD	1.10±0.58	0.86±0.72	0.22
% of predicted value±SD	29.9±13.9	27.6±22.1	0.65
Alteration in FEV1/FVC			
%±SD	1.2±10.1	2.5±11.8	0.69

FEV1: forced expiratory volume in the first second; FVC: forced vital capacity; IVA: intravenous analgesia; TEA: thoracic epidural analgesia; SD: standard deviation

in the IVA group, while reduction in the FEV1/FVC ratio was comparable among the treatment arms (Table 2).

According to the blood gas analysis results, the mean pH values of patients were significantly lower in the IVA group at 1 and 72 hours (p=0.008 and p=0.02, respectively). The mean bicarbonate values of the patients in the IVA group were again significantly lower in the IVA group in the 1st hour (mEq/dL 22.8±4.3 vs. 25.4±5.1, p=0.009). The differences in the mean values of PO_2, PCO_2, pH, and bicarbonate levels between the groups are illustrated with stacked line charts in Figure 3.

DISCUSSION

Thoracic surgery frequently causes intense pain, which restricts early ambulation. If proper analgesia cannot be provided, it is commonly associated with severe respiratory complications (via reduction of tidal volumes) and delayed discharge [1, 3, 7, 9, 10]. The incision itself, intercostal neural damage, chest wall inflammation, pulmonary parenchymal injury, and prolonged duration of drainage via chest tubes are the main reasons for early postoperative pain [10-12]. TEA is an effective method for decreasing the intensity of pain. It was also proved that TEA reduces pulmonary complications (including respiratory depression, pneumonia, and so on), length of hospital stay, and other components of perioperative morbidity [7, 9, 13, 14]. TEA facilitates deep breathing by reducing the severity of pain and attenuating the reflex inhibition of diaphragmatic movement. Hence, it provides early recovery of respiratory volumes, encourages expectoration, and enhances adaptation to physiotherapy [2, 9, 10, 15]. Despite these advantages, reversible adverse effects of TEA, such as hypotension and urinary retention as

RESULTS

The mean age of the study population was 56.8±7.5 years (men constituting 92% of the population). TEA was used in 27 (43.5%) patients. In 5 (8.1%) patients, a complication attributed to the procedure was observed. These were arrhythmias (2 patients), prolonged air leak (2 patients), and significant bleeding requiring transfusion (1 patient). The postoperative median values and ranges of VAS-R and VAS-C of the patients at first 72 hours are displayed in Figures 1 and 2.

Patient demographics were comparable between the groups. The differences in the operational data (type of operation, procedure time, duration of tube drainage, and complication rate) between the groups were not statistically significant. Preoperative FEV1 and FVC values were numerically lower in the TEA group, but these differences did not reach statistical significance either. These comparisons are shown in Table 1. Reductions in the FEV1 and FVC were insignificantly higher

well as the risk of epidural hematoma and irreversible neural injury, should be considered [1, 2].

Harris et al. [16] have demonstrated a close relationship between pain scores (particularly with deep breathing) and incentive spirometry performance. They have also claimed that spirometry performance can be used as an indicator of effective analgesia.

TEA has a transient detrimental effect on the contribution of parasternal intercostal muscles to breathing and rib cage movement. However, the diaphragmatic function remains unchanged. Hence, TEA reduces most of the lung volumes including FEV1 and FVC (approximately, 12% for both) [10]. However, subsequent hypoxia is not an expected clinical end point for patients in whom TEA was administered instead of opioid-based IVA [10, 17, 18]. Jung et al. [18] have reported that TEA with bupivacaine, epidural sufentanil, and total IVA regimen involving remifentanil infusion, had comparable effects on parameters of oxygenation and shunt fraction in patients undergoing thoracotomy with one-lung ventilation. Therefore, they have concluded that the level of sympathetic blockage provided by analgesia does not have a profound effect on oxygenation.

Behera et al. [17] have compared patient-controlled TEA with bupivacaine and opioid combinations and intravenous morphine for early postoperative outcome in thoracotomy. They have stated that PO_2 and PCO_2 were similar between the groups, although the reduction in FVC and peak expiratory flow rate (PEFR) values was more explicit in the intravenous morphine group. They also noted that their study lacked the statistical power to claim that TEA was superior to IVA by preserving early postoperative pulmonary functions. Another study compared the efficacy of TEA and conventional analgesia for off-pump coronary artery bypass surgery in patients with chronic obstructive pulmonary disease. The authors revealed that in the TEA group, improvement in FVC and FEV1 was significantly higher, starting from 6 hours and 2nd day postoperatively, respectively. Clinical end points, such as the length of intensive care unit and hospital stay, mortality, reintubation, and myocardial infarction, were similar. In the arterial blood gas analysis performed after extubation, PO_2 and pH values were higher (p<0.001 and p=not significant, respectively) and mean PCO_2 was lower (p<0.001) in the TEA arm of this study [19]. Per these findings, in our study, deterioration of early FEV1 and FVC values was less evident if TEA was chosen as the pivotal mode of analgesia. Nevertheless, partial CO_2 and O_2 pressures in blood gas analysis were similar between the treatment arms despite the distinction in respiratory volumes. In the IVA group, pH values were consistently lower in our study. As the mean partial CO_2 pressures were comparable, this difference might be explained by a metabolic alteration. Long procedural time, hypothermia, fluid restriction, and drug-induced hypotension may contribute to this tendency. This effect might be particularly profound immediately after the operation. We believe that the difference in pH values during the follow-up period did not yield clinical significance because all the values were within acceptable ranges.

Efficacy of TEA on postoperative respiratory parameters was also checked against other regional analgesia techniques.

Meierhenrich et al. [20] have compared the intercostal nerve block plus patient-controlled analgesia with morphine and TEA with ropivacaine. In the TEA group, FEV1, FVC, and PEFR values were significantly higher in the early postoperative days. However, a comparison of TEA with paravertebral block (PVB) yielded conflicting results. Several studies have revealed that analgesia with both methods resulted in similar oxygenation parameters and spirometric volumes [21-23]. Richardson et al. [24] have reported that PEFR and oxygen saturation were better preserved in the PVB group of their sample population. Mehta et al. [25] have compared these methods in robotic-assisted coronary artery bypass surgery and stated that pulmonary function tests FEV1, FVC, PEFR, and maximum ventilatory volumes showed marginally better (statistically nonsignificant) results in the PVB group. In contrast to these data, Messina et al. [26] have reported significantly better preservation of FVC in the TEA group during the early postoperative period.

The severity of postoperative pain was also found to be associated with the technique used for surgical exploration and suturing in various investigations, and muscle sparing surgery was demonstrated to be superior to conventional posterolateral thoracotomy [15]. However, Celikten et al. [27] did not find a significant difference when they compared anterior with posterolateral thoracotomy in the same context. Regarding rib closure, transcostal suturing was claimed to be less painful than conventional pericostal suturing. In this study, the authors noted that postoperative reduction in FVC, FEV1, and PEFR values was more profound with the latter method [28]. Posterolateral thoracotomy and pericostal suturing were used in our sample population with the intent of eliminating surgical technique-related bias.

In this study, preemptive analgesia and postoperative multimodal analgesia, either with TEA or opioid-based IVA, were used for warranting definite in-hospital pain relief after thoracotomy. In our sample population, patients in the TEA group had marginally lower VAS-R and VAS-C scores during the first 72 hours of follow-up. Most of these differences reached statistical significance or remained at borderline.

The management of thoracotomy pain is sophisticated and requires modification of various pathways. Thus, using regional and systemic modes of analgesia in combination is mandatory to achieve that goal, thereby not only enhancing the quality of life but also preserving respiratory functions and decreasing the frequency of early postoperative complications [7, 29].

Our study had some limitations, one of which was the relatively small size of the sample population. Another limitation was that this was a single-center study conducted over a limited time period. In addition, proper positioning of the epidural catheters was not verified with an imaging modality. Finally, the difference in the mean pH values of the groups could not be precisely clarified. Our study lacked the power to determine the exact reason for this discrimination as the relevant perioperative variables were not recorded. The study focused only on the recovery of the respiratory function in the early postoperative period.

In conclusion, this study was designed for evaluating the efficacy of TEA against opioid-based IVA, focusing on early postoperative respiratory functions and arterial blood gas analysis parameters. In the TEA group, subjective pain perception was lower in our sample population; however, we could not verify the superiority of TEA over IVA through better preservation of lung volumes and oxygenation parameters. There was a tendency for lower reduction of FEV1 and FVC on the third postoperative day in the TEA group. In the IVA group, the mean pH values of the patients were significantly lower in the same period.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital (12.05.2015; 2866/2015/29).

Informed Consent: Informed consent was received from all participants.

Author Contributions: Concept - D.Ö.O., N.Ç.; Design - D.Ö.O., N.Ç., Ö.İ., A.S.; Supervision - S.B., A.S.; Resources - A.U., S.B., Ö.İ., M.V.D., Ç.O., A.S.; Materials - D.Ö.O., N.Ç, A.U., Ç.O., M.V.D.; Data Collection and/or Processing - D.Ö.O., A.U., Ç.O., M.V.D.; Analysis and/or Interpretation - D.Ö.O., N.Ç., Ö.İ.; Literature Review - D.Ö.O.; Writing - D.Ö.O., N.Ç.; Critical Review - S.B., A.S.

Conflict of Interest: The authors have no conflicts of interest to declare.

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