

# Timelog-Based Approach to Early Post-Thoracotomy Pain in Lung Cancer Surgery

## Akciğer Kanseri Cerrahisinde Torakotomi Sonrası Erken Dönem Ağrıya Zaman Akışı Temelli Yaklaşım

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**ABSTRACT Objective:** Postoperative pain is a major concern about thoracotomy and acts a determinant of quality of life and complication occurrence. Here we sought to distinctively assess the predictors of significant pain in the 1<sup>st</sup>, 6<sup>th</sup>, and 12 hours of elective lung cancer surgery. **Material and Methods:** Seventy American Society of Anesthesiologists (ASA) 1-3 patients who were performed posterolateral thoracotomy by the same surgical team were retrospectively recruited. Perception of pain was quantified by Visual Analogue Scale (VAS) and VAS scores of 1<sup>st</sup>, 6<sup>th</sup> and 12<sup>th</sup> hours were recorded and a score of four or higher was identified as significant pain. Postoperative analgesia was provided either by thoracic epidural analgesia (TEA) with 0.1% bupivacaine or pethidine-based intravenous analgesia (IVA) in our sample population. **Results:** Regarding demographic characteristics, there were almost no significant differences among groups with and without significant pain (Group Significant Pain, SP, and Group Tolerable Pain, TP; respectively) at the first 12 hours. Exceptions were the presence of higher rates of iatrogenic rib fracture (p=0.02) and operation related complications (p=0.046) in Group SP at 1<sup>st</sup> and 6<sup>th</sup> hours respectively. The frequency of patients treated with IVA was significantly higher in SP group at 1<sup>st</sup> and 6<sup>th</sup> hours but not at 12<sup>th</sup> hour. **Conclusion:** Type of analgesia was solely detected to be a persistent determinant of significant pain after lung cancer surgery. However, this was valid for only the first six hours.

**Keywords:** Analgesia, epidural; pain measurement; thoracotomy

**ÖZET Amaç:** Postoperatif ağrı torakotomiye ilişkin temel bir sorundur; ve sadece yaşam kalitesinde değil komplikasyon görülme sıklığında da belirleyici rol oynar. Bu çalışmada elektif akciğer kanser cerrahisi sonrası 1,6 ve 12. saatlerde kaydedeğer ağrıyı predikte eden etkenlerin birbirinden ayrı olarak tespit edilmesi hedeflenmiştir. **Gereç ve Yöntemler:** Aynı cerrahi ekip tarafından posterolateral torakotomi ile opere edilen 70 Amerikan Anesteziyoloji Derneği (ASA) 1-3 hastanın verileri retrospektif olarak incelendi. Vizüel Analog Skalası (VAS) ile sayısallaştırılan ağrı algısına dair skorların 1, 6 ve 12. saatlerdeki değerleri kaydedildi ve dört ve üzeri değerler kaydedeğer ağrı olarak nitelendi. Postoperatif analjezi ya %0,1'lik bupivakainle torasik epidural analjeziyle (TEA); ya da petidin temelli intravenöz analjeziyle (İVA) sağlandı. **Bulgular:** İlk 12 saatte kaydedeğer ağrısı (Grup KA) olan ve olmayan (Grup Dayanılabilir Ağrı; DA) gruplar arasında demografik özellikler açısından hemen hiç belirgin fark yoktu. İstisnalar ise sırasıyla 1. ve 6. saatlerde iyatrojenik kot kırıklarının (p=0,02) ve operasyonla ilişkili komplikasyonların (p=0,046) Grup KA'da daha fazla olmasıydı. Kaydedeğer ağrı grubunda İVA ile tedavi edilen hastaların oranı 1. ve 6. saatte anlamlı olarak fazlayken 12. saatte anlamlı fark yoktu. **Sonuç:** Akciğer kanseri cerrahisi sonrası kaydedeğer ağrı varlığını öngördürme konusunda analjezi yönteminin süregelen bir belirteç olduğu ancak bu durumun sadece ilk altı saat için geçerli olduğu sonucuna varıldı.

**Anahtar Kelimeler:** Analjezi, epidural; ağrı ölçümü; torakotomi

Postoperative pain is a determinant of quality of life and complication occurrence after thoracotomy.<sup>1-3</sup> Impaired chest wall integrity, rib fractures, intercostal neural damage and alteration of nociception are the main factors determining the intensity of pain.<sup>1,2,4</sup> Systemic analgesia and regional analgesia techniques can be utilized separately or as a combination treatment to provide adequate pain relief. Regional analgesia was frequently used at the last 20 years since its safety and efficacy was

demonstrated in several investigations with individual designs.<sup>1,5,6</sup> Thoracic epidural analgesia (TEA), paravertebral blockade, intercostal neural blockade, and subpleural analgesia can be listed as the main regional analgesia techniques.<sup>3,6-10</sup> Thoracic epidural analgesia is accepted as the gold standard and has a proven advantage regarding influence on physiologic response and efficacy as compared to other techniques.<sup>1,6,9,11,12</sup>

The main purpose of our study was to determine the predictors of significant pain (including the method of analgesia) during surgical critical care follow-up of post-thoracotomy patients in a single tertiary center. We aimed to highlight the entity of time-log instead of technical issues and patient-related factors considering the fact that relevant variables which might provoke or alleviate the perception of pain were not persistent throughout the early postoperative period.

## MATERIAL AND METHODS

### STUDY DESIGN AND PATIENT SELECTION

Patient files of the individuals who had been operated with posterolateral thoracotomy by the same surgical team in a tertiary center for thoracic surgery between February 2015 and May 2016 were evaluated. Seventy adult lung cancer patients who met inclusion criteria were enrolled. The study was approved by the ethics committee of University of Health Sciences Yedikule Respiratory Diseases and Thoracic Surgery Training and Research Hospital (28/04/2015, 2866) and therefore had been performed in accordance with global ethical standards. Permission for utilization of the data was granted from the hospital administration and informed consent was received from the participants.

Patients who had determined psychiatric problems, auditory deficit, history of drug abuse, severe cardiovascular system disorders or severe respiratory depression (depicted as having less than 50% of the predicted value of forced expiratory volume) were excluded.

Operating room logs were checked and procedures with serratus anterior muscle and chest wall resection were determined. These patients were also excluded even though they had met other qualifications. Finally, patients who could not be extubated before transfer were not involved, regarding the possibility of being ineligible for early postoperative pain assessment.

Outpatient anesthesia clinic, preoperative evaluation logs were examined. Age, gender, height and weight (body mass index (BMI) and body surface area (BSA) were calculated later), smoking status (package/years) of patients were noted. Social status including the level of education, marriage status, and occupation was noted if they existed in preoperative patient identification forms of nurses. Missing data were collected by phone calls. Localization, histologic type, and size of the tumor and ASA score were additionally recorded.

### FEATURES OF ANESTHETIC TECHNIQUE AND INTRAOPERATIVE ANALGESIA

Following our institutional habits, postoperative analgesia was provided by multimodal analgesia in our sample population selecting either TEA or pethidine-based intravenous analgesia (IVA) as the pivotal method. We appreciate the concerns about possible bias about standard application of the methods in consideration of the retrospective nature of the study. However, pre-defined anesthetic regimens were administered during the procedures and exceptional cases were excluded if any uncertainty or significant variation had existed. The pivotal method of analgesia was selected according to anesthesiologist's discretion and patient's will.

For TEA, before initiation of the operation, an epidural catheter was inserted by the loss of resistance method at the level of T3-T7 with the help of an 18 G Tuohy needle (Pajunk, Geisingen, Germany) while the patient was in sitting position. After verification of proper positioning, 10 ml bolus dose of 0.1% *Bupivacaine* was injected. Analgesia maintenance was provided by infusion of 0.1% *Bupivacaine* (0.1 ml/kg/hour) both intraoperatively and postoperatively for 24 hours.

Anesthesia was induced with *midazolam*, *propofol*, and *fentanyl*. The neuromuscular blockage was provided with *cisatracurium besylate*. A double-lumen tracheal tube was inserted thereafter. After standard patient positioning, localization of the tube was checked with fiberoptic bronchoscopy. Pressure controlled ventilation was used (Primius, Dräger, Luebeck, Germany) and invasive arterial pressure, electrocardiography, arterial blood gas analysis, end-tidal carbon dioxide concentration, central venous pressure and urine output were closely monitored in the operating room. Hypothermia was avoided with the help of a warming system and body temperature was kept over 36°C. If the pivotal method was TEA, absolute intraoperative anesthesia maintenance was warranted with *sevoflurane* in addition to TEA. If it was IVA, *remifentanyl* infusion (0.1-0.2 mcg/kg/min) and 0,5-2 MAC *sevoflurane* combination were used instead. *Remifentanyl* induced postoperative hyperalgesia was avoided by gradually reducing the dose in the last hour of operation as previously recommended.<sup>13</sup> *Remifentanyl* infusion was ceased before awakening.

The intercostal blockade was invariably applied by the surgical team to the entire population before closing the wound by injecting 4 ml of 0.25% *bupivacaine* to the region of incision and two intercostal regions above and below the incision site. Once closure was started, *morphine sulfate*, *tramadol*, *paracetamol* and *tenoxicam* was given intravenously to intensify early postoperative analgesia. Anterior 28 Fr and posterior 32 Fr drainage tubes were inserted to the patients to whom lobectomy or bilobectomy was performed. For pneumectomy, only posterior 32 Fr tube was placed. After reversal of neuromuscular blocking agents, patients with adequate spontaneous ventilation and verbal response were transferred to the surgical critical care unit.

Regarding peri-operative data, procedure time, the number of drainage tubes, type of the operation (lobectomy, pneumectomy, etc.), thoracotomy level, presence of iatrogenic costal damage or other operation-related complications were collected from log files of the operating room.

## ASSESSMENT OF PAIN

Visual Analogue Score (VAS) was used to estimate the severity of pain. A score of 0 cm represented “no pain at all” and 10 cm did “intractable pain” so.<sup>3</sup> Thoracic pain was assessed by a nurse and entered in a critical care log file. Visual Analogue Scale scores 1<sup>st</sup>, 6<sup>th</sup> and 12<sup>th</sup> hours of the early postoperative period were noted from these files.

## POSTOPERATIVE ANALGESIA MANAGEMENT

For TEA, *bupivacaine* infusion was administered through the epidural catheter as described above. Intravenous *pethidine* infusion (0.25 mg/kg/hour) was chiefly used for IVA. It was administered for 24 hours at the surgical critical care unit. Patients in both groups, additionally received *paracetamol* (15 mg/kg, 1000 mg at max) at every 6 hours and *tenoxicam* (20 mg) at every 12 hours via intravenous route.

A VAS score lower than 4 was defined as tolerable pain as previously described.<sup>2,9,14</sup> For scores equal to or over 4, patients treated with TEA received an additional bolus dose of 10 ml 0.1% *bupivacaine*. Infusion rate was also increased by 2 ml/hour. If the patient was treated with IVA, an additional bolus dose of 0.5 mg/kg *pethidine* was given. Infusion rate was also increased by 0.35 mg/kg/hour.

Cases were clustered according to the severity of pain. Patients with a VAS score of 4 or higher were allocated to Group SP (significant pain). Remaining patients were allocated to Group TP (tolerable pain). The data of these groups were distinctively analyzed at 1<sup>st</sup>, 6<sup>th</sup> and 12<sup>th</sup> hours to determine the predictors of significant pain at the relevant time section.

## STATISTICAL ANALYSIS

The data were presented as mean ± SD and median (maximum-minimum) for continuous variables and as percentage (number of cases) for categorical variables. Normal distribution was tested with Kolmogorov-Smirnow test. It was also confirmed by histograms. Unpaired t-test was used to test the difference between the continuous variants which showed normal distribution between the two

groups. Mann-Witney U test was used to compare two-group non-normally distributed variables. Pearson Chi-square, Fisher's exact test, and Continuity Correction (Yate's Correction) test were used to test the categorical variants.

Univariate analyses for 1<sup>st</sup>, 6<sup>th</sup> and 12<sup>th</sup> hours VAS score were conducted separately. In order to predict hour-specific predictors of VAS scores, the variables which were significant at %10 level in univariate statistics were further evaluated with multivariate logistic regression analysis (Enter Model). The results of the model were reported as odds ratio (OR), 95% Confidence Interval, beta, and p values.

A p value of < 0.05 was considered statistically significant. Statistical Package for the Social Sciences (SPSS version 22.0, SPSS Inc., Chicago, IL, USA) was used to perform these analyses.

## RESULTS

A study population consisting of 70 individuals were evaluated. For the first hour comparison, data of 3 patients were not involved due to missing values of several variables. The mean age of the study population was 62.1 and 27 (38.6%) of the patients were over 65 years old. Male patients were constituting 92.8% of the participants. Thoracic epidural analgesia was performed in 30 patients (42.8%). Operation-related complications were observed in 13 patients (18.6%) and distribution of them was as follows:

- Arrhythmias (6 patients)
- Prolonged air leak (4 patients)
- Significant bleeding requiring transfusion (2 patients)
- Acute renal failure (1 patient)

Postoperative median values and ranges of VAS score of the patients at 1<sup>st</sup>, 6<sup>th</sup> and 12<sup>th</sup> hours were 3 (7-0), 2 (7-0), and 2 (7-0); respectively.

Regarding patient demographics (including age, gender, BMI, smoking history, level of education, marriage, and occupational status) only ASA score was found to be significantly different

between study groups at the 6<sup>th</sup> hour. The frequency of ASA II patients was lower and that of ASA III patients was higher in Group TP (p=0.043) (Table 1).

Most of the operational data (tumor specifications, thoracotomy level, type of operation, operation length) were comparable between groups at all levels (Table 1, Table 2, Table 3). Presence of iatrogenic rib fracture and procedural complications were associated with significant pain at 1<sup>st</sup> and 6<sup>th</sup> hours, respectively. These were designated as significant predictors of significant pain for the relevant time section (absence of rib fracture for tolerable pain;  $\beta$ :1.46, p=0.02, OR:4.31, 95% CI [1,259-14,749] and presence of an operative complication for severe pain;  $\beta$ :1.56, p=0,046, OR: 4,74, 95% CI [1,031-21,786]).

The frequency of the patients to who were performed TEA was significantly higher in Group TP in the first 6 hours (Figure 1). Association of TEA with tolerable pain was confirmed by multivariate analyses at the respective timeline (Table 1, Table 2, Table 3).

At 12<sup>th</sup> hour, the difference of parameters between groups did not reach the level of significance, thus no variable could be established as an independent predictor.

## DISCUSSION

Thoracic surgery results in an intense and mostly intolerable postoperative pain, which is frequently associated with severe respiratory complications and delayed discharge especially if it is not properly treated.<sup>1-3,5,7</sup> In addition to incisional pain, intercostal neural damage, chest wall inflammation, pulmonary parenchymal injury, central nervous system sensitization, insertion of chest tubes, and prolonged duration of drainage determine the degree of cumulative pain perception.<sup>2,4,15</sup>

There is no known relationship between personal specifications, lesion-related features, type of operation and intensity of early postoperative pain.<sup>11</sup> Peng et al. denoted that age>60 years, female gender and hypertension might be associated with chronic pain. However, in this study prolonged

**TABLE 1:** Distribution of the patients according to severity of pain at sixth hour.

	Group TP (VAS-R<4) n=55	Group SP (VAS-R ≥ 4) n=15	P Value
Age (years), Mean ± SD	61±7	59±10	0.288
Male gender, n (%)	51 (92.7)	14 (93.3)	1
BMI (kg/m <sup>2</sup> ), Mean ± SD	25±4.2	26±3.6	0.227
BSA (m <sup>2</sup> ), Mean ± SD	1.84±0.16	1.90±0.17	0.254
Smoking (package/year), Median (Range)	40 (150-10)	40 (120-4)	0.804
Education, n (%)			0.413
None	4 (7.3)	0 (0)	
Primary School	37 (67.3)	12 (80)	
High School	10 (18.2)	1 (6.7)	
Licence and above	4 (7.3)	2 (13.3)	
Marital status, n (%)			0.637
Single	5 (9.1)	2 (13.3)	
Married	50 (90.9)	13 (86.7)	
Occupation, n (%)			0.821
None	7 (12.7)	2 (13.3)	
Freelance	19 (34.5)	7 (46.7)	
Worker	11 (20)	3 (20)	
Officer	3 (5.5)	0 (0)	
Retired	15 (27.3)	3 (20)	
ASA score, n (%)			0.043*
ASA 1	1 (1.9)	1 (6.7)	
ASA 2	27 (50)	12 (80)	
ASA 3	26 (48.1)	2 (13.3)	
Tumor Localization, n (%)			0.186
Right Inferior-middle	11 (20)	7 (46.7)	
Right Superior	11 (20)	3 (20)	
Left Inferior	14 (25.5)	2 (13.3)	
Left Superior	19 (34.5)	3 (20)	
Estimated Tumor Volume (cm <sup>3</sup> ), Median (Range)	31 (459.4-1.40)	21 (263-1.95)	0.812
Operation Duration (min), Median (Range)	350 (480-120)	340 (500-240)	0.375
More than One Drainage Tubes n (%)	23 (41.8)	5 (33.3)	0.767
Operation Type, n (%)			0.758
Lobectomy	39 (70.9)	10 (66.7)	
Pneumectomy	16 (29.1)	5 (33.3)	
Thoracotomy level, n (%)			0.561
4th Rib	1 (1.8)	0 (0)	
5th Rib	51 (92.7)	15 (100)	
6th Rib	3 (5.5)	0 (0)	
Pathologic Subtype (%)			0.795
Squamous	28 (5.8)	9 (60)	
Adenocarcinoma	13 (25)	4 (26.7)	
Others	11 (21.1)	2 (13.3)	
Analgesia technique, n (%)			0.017*
IVA	27 (49.1)	13 (86.7)	
TEA	28 (50.9)	2 (13.3)	
Presence of iatrogenic rib fracture, n (%)	19 (34.5)	4 (26.5)	0.565
Presence of operation related complication, n (%)	7 (12.7)	6 (40)	0.026*
<b>Regression analyses</b>	<b>B</b>	<b>OR, 95% CI</b>	<b>P value</b>
Analgesia technique	1.753	5.774, [1.062-31.389]	0.042*
Operation related complication	1.556	4.739, [1.031-21.786]	0.046*
ASA score			
ASA I	N/A	N/A	N/A
ASA II	-0.629	0.533, [0.029-9.941]	0.673
ASA III	-2.607	0.074, [0.003-1.907]	0.116

Results of the multivariate analyses were displayed at the bottom of the table. (\*) represents statistical significance. IVA: Intravenous analgesia, TEA: Thoracic epidural analgesia, BMI: Body mass index, BSA: Body surface area, ASA: American Society of Anesthesiologists.

**TABLE 2:** Distribution of the patients according to severity of pain at first hour.

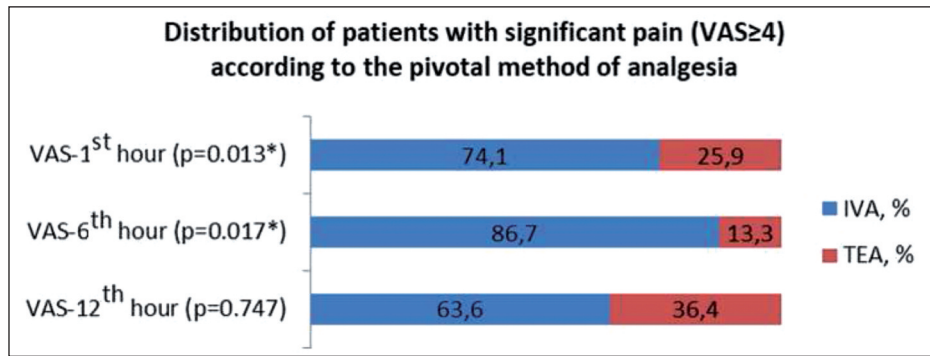
	Group TP ( VAS<4) n=40	Group SP (VAS-R ≥ 4) n=27	P Value
Age (years), Mean ± SD	62±7.7	60 ± 8.7	0.367
Male gender, n (%)	38 (95)	24 (88.9)	0.385
BMI (kg/m <sup>2</sup> ), Mean ± SD	24.7±3.8	26.3± 4.5	0.139
BSA (m <sup>2</sup> ), Mean ± SD	1.82± 0.14	1.89±0.19	0.150
Smoking (package/year), Median (Range)	40 (150-10)	40 (120-4)	0.687
Education, n (%)			0.333
None	3 (7.5)	0 (0)	
Primary School	26 (65)	21 (77.8)	
High School	8 (20)	3 (11.1)	
Licence and above	3 (7.5)	3 (11.1)	
Marital status, n (%)			1
Single	4 (10)	3 (11.1)	
Married	36 (90)	24 (88.9)	
Occupation, n (%)			0.137
None	5 (12.5)	4 (14.8)	
Freelance	15 (37.5)	9 (33.3)	
Worker	11 (27.5)	3 (11.1)	
Officer	0 (0)	3 (11.1)	
Retired	9 (22.5)	8 (25.4)	
ASA score, n (%)			0.594
ASA 1	1 (2.6)	0 (0)	
ASA 2	22(55)	17 (63)	
ASA 3	17(43.6)	10 (37)	
Tumor Localization, n (%)			0.290
Right Inferior-middle	10 (25)	8 (29.6)	
Right Superior	6 (15)	7 (25.9)	
Left Inferior	12 (30)	3 (11.1)	
Left Superior	12 (30)	9 (33.3)	
Estimated Tumor Volume (cm <sup>3</sup> ), Median (Range)	36.8 (459.4-2.1)	26.3 (240-1.4)	0.387
Operation Duration (min), Median (Range)	350 (480-120)	360 (500-180)	0.344
More than One Drainage Tubes n (%)	18 (45)	8 (29.6)	0.205
Operation Type, n (%)			0.564
Lobectomy	27 (67.5)	20 (74.1)	
Pneumectomy	13 (32.5)	7 (25.9)	
Thoracotomy level, n (%)			0.460
4th Rib	1 (2.5)	0 (0)	
5th Rib	38 (95)	25 (92.6)	
6th Rib	1 (2.5)	2 (7.4)	
Pathologic Subtype (%)			0.674
Squamous	21 (56.8)	15 (55.6)	
Adenocarcinoma	8 (21.6)	8 (29.6)	
Others	8 (21.6)	4 (14.8)	
Analgesia technique, n (%)			0,013*
IVA	17 (42.5)	20 (74.1)	
TEA	23 (57.5)	7 (25.9)	
Presence of iatrogenic rib fracture, n (%)	18 (45)	5 (18.5)	0.036*
Presence of operation related complication, n (%)	7 (17.5)	5 (18.5)	1
<b>Regression analyses</b>	<b>B</b>	<b>OR, 95% CI</b>	<b>P value</b>
Analgesia technique	1.507	4.512, [1.457-13.967]	0.009*
Iatrogenic rib fracture	1.461	4.308, [1.259-14.749]	0.020*

Results of the multivariate analyses were displayed at the bottom of the table. (\*) represents statistical significance. IVA: Intravenous analgesia, TEA: Thoracic epidural analgesia, BMI: Body mass index, BSA: Body surface area, ASA: American Society of Anesthesiologists.

**TABLE 3:** Distribution of the patients according to severity of pain at twelfth hour.

	Group TP (VAS-R<4) n=59	Group SP (VAS-R ≥ 4) n=11	P Value
Age (years), Mean ± SD	61±7	61±11	0.996
Male gender, n (%)	55 (93.2)	10 (90.9)	1
BMI (kg/m <sup>2</sup> ), Mean ± SD	25±4.3	25±3.1	0.773
BSA (m <sup>2</sup> ), Mean ± SD	1.85 ± 0.16	1.88 ± 0.18	0.569
Smoking (package/year), Median (Range)	40 (150-4)	38.5 (135-20)	0.576
Education, n (%)			0.711
None	4 (6.8)	0 (0)	
Primary School	40 (67.8)	9 (81.8)	
High School	10 (16.9)	1 (9.1)	
Licence and above	5 (8.5)	1 (9.1)	
Marital status, n (%)			1
Single	6 (10.2)	1 (9.1)	
Married	53 (89.8)	10 (90.9)	
Occupation, n (%)			0.503
None	7 (11.9)	2 (18.2)	
Freelance	20 (33.9)	6 (54.5)	
Worker	12 (20.3)	2 (18.2)	
Officer	3 (5.1)	0 (0)	
Retired	17 (28.8)	1(9.1)	
ASA score, n (%)			0.138
ASA 1	1 (1.7)	1 (9.1)	
ASA 2	31 (53.4)	8 (72.7)	
ASA 3	26 (44.8)	2 (18.2)	
Tumor Localization, n (%)			0.975
Right Inferior-middle	15 (25.4)	3 (27.3)	
Right Superior	12 (20.3)	2 (18.2)	
Left Inferior	13 (22)	3 (27.3)	
Left Superior	19 (32.2)	3 (27.3)	
Estimated Tumor Volume (cm <sup>3</sup> ), Median (Range)	31 (459.4-1.40)	42 (263-2.08)	0.712
Operation Duration (min), Median (Range)	350 (500-120)	330 (480-180)	0.955
More than One Drainage Tubes n (%)	22 (37.3)	6 (54.5)	0.328
Operation Type, n (%)			0.723
Lobectomy	42 (71.2)	7 (63.6)	
Pneumectomy	17 (28.8)	4 (36.4)	
Thoracotomy level, n (%)			0.673
4th Rib	1 (1.7)	0 (0)	
5th Rib	55 (93.2)	11(100)	
6th Rib	3 (5.1)	0 (0)	
Pathologic Subtype (%)			0.375
Squamous	30(53.6)	7 (63.6)	
Adenocarcinoma	16 (28.6)	1 (9.1)	
Others	10 (17.9)	3 (27.3)	
Analgesia technique, n (%)			0.747
IVA	33 (55.9)	7 (63.6)	
TEA	26 (44.1)	4 (36.4)	
Presence of iatrogenic rib fracture, n (%)	20 (33.9)	3 (27.3)	1
Presence of operation related complication, n (%)	10 (16.9)	3 (27.3)	0.416

IVA: Intravenous analgesia, TEA: Thoracic epidural analgesia, BMI: Body mass index, BSA: Body surface area, ASA: American Society of Anesthesiologists.



**FIGURE 1:** Distribution of the patients with significant pain (VAS  $\geq$  4) in relevant time section according to the pivotal method of analgesia. “\*” designates significant difference. IVA: Intravenous analgesia, TEA: Thoracic epidural analgesia, VAS: Visual analogue scale.

drainage from chest tubes was established as the only independent predictor of chronic pain with a neuropathic component.<sup>15</sup> Keeping in line with this data, in our sample population, none of the personal, disease or operation-related features were associated with pain intensity.

Different surgical exploration and suturing techniques were also tested with the intention to reduce postoperative pain. The superiority of muscle-sparing surgery over conventional posterolateral thoracotomy for pain severity was demonstrated.<sup>11</sup> Besides that, Celikten et al. did not find a significant difference when they compared anterior and posterolateral thoracotomy with the same purpose.<sup>16</sup> Rib closure technique also matters. Transcostal suturing and double edge closure were found to be less painful as compared to conventional pericostal suturing.<sup>17-19</sup> In our study, surgical procedures were invariably performed with muscle-sparing posterolateral thoracotomy and thoracic cavity was closed with pericostal suturing.

Taking all abovementioned facts into account, providing effective analgesia preferably with multiple modalities is of critical importance for the management of thoracotomy pain. Effective analgesia may provide not only an increased quality of life but also reduce the frequency of complication occurrence at early postoperative period.<sup>2,7,20</sup> In our daily routine, we prefer multimodal analgesia for definite in-hospital pain relief. In our center, TEA or IVA with *pethidine* is

used as pivotal analgesic methods. Intercostal blockade is routinely applied. Agents like *morphine sulfate*, *tramadol*, *paracetamol*, and *tenoxicam* are used for bridging between intraoperative and postoperative analgesia.

Another issue that may have altered early postoperative pain perception was the utilization of *remifentanyl* as a component of IVA. This agent was used to trigger postoperative hyperalgesia, particularly at first two hours. However, using lower doses of the drug intraoperatively and gradual withdrawal at the end of the operation were reported to reduce additional analgesic demand at early postoperative period.<sup>13,21,22</sup>

Inadequate treatment of post-thoracotomy pain may also lead to pulmonary complications (atelectasis, pneumonia, respiratory depression, and reintubation, etc.) due to restricted deep breathing, reduced ability of expectoration and inability to adapt physiotherapy.<sup>10,11,18</sup> In our sample population, only VAS score at 6<sup>th</sup> hour was significantly associated with perioperative complication occurrence.

Intravenous analgesia based on abundant utilization of opioid analgesics remained as the mainstay of treatment for years until the introduction of modern regional analgesia methods. Intravenous analgesia is still a preferred modality for pain control after thoracotomy considering some advantages like lower rates of serious complications and technical ease. Jin et al.



reported similar pain control with TEA (*ropivacaine* and *sufentanil* combination) and IVA comprising *tramadol* and *lornoxycam* combination until the postoperative 4<sup>th</sup> day.<sup>23</sup> Intravenous *pethidine* was also tested against intercostal blockade with *bupivacaine* and TEA with *fentanyl*. In the former intercostal blockade provided better analgesic effect than IVA at the second and third postoperative days but not on the first day.<sup>24</sup> In the latter first postoperative day pain scores were higher in the TEA group. However, pain scores were comparable at the next two days. Surprisingly, patients treated with TEA required additional analgesics more frequently than the IVA group in this study.<sup>25</sup>

Although conflicting results existed in the literature, TEA proved its efficacy over conventional analgesia and other regional techniques.<sup>1-3,6-9,26,27</sup> Reducing the requirement for rescue analgesics, sustained mode of action and relatively low incidence of serious procedure-related complications are the main advantages of TEA, which made it accepted as the gold standard method.<sup>1,6,9</sup> Along with these, TEA has superiority over conventional analgesia through preserving cardiopulmonary functions, diminishing stress response, facilitating the recovery of gastrointestinal motility and improving immune function.<sup>5,7,9,11,12</sup>

Nevertheless, the risk of irreversible neural damage (~1:10000 in the literature) and relatively high frequency of other treatable conditions like hypotension raised the necessity of developing less invasive techniques.<sup>1,7,10</sup> Paravertebral blockade, intercostal blockade, and subpleural analgesia were most commonly compared with TEA within this context.<sup>1,8-10,28</sup> Among these, only efficacy of paravertebral blockade was comparable with TEA for adequate analgesia at the early postoperative period. Nevertheless, the results of these investigations were equivocal due to diversities of the study designs.<sup>1,12,28,29</sup> Eventually, absolute evidence indicating the superiority of minimally invasive techniques over TEA does not exist.

There is strong evidence supporting the protective effect of TEA from cardiovascular adverse events, respiratory complications, and ileus. However, most of these beneficial effects were pronounced in high-risk procedures like thoracotomy and upper abdominal surgery, and only if a local anesthetic agent but not an opioid was utilized.<sup>7</sup> On the other hand, the relationship of local anesthetic and opioid mixtures with decreased length of hospitalization and perioperative morbidity was also reported.<sup>30</sup> In our facility, administration of *bupivacaine* alone via epidural catheter was preferred.

Providing central analgesia before the arrival of noxious stimuli leads to an increase in the threshold of pain perception at the receptor level.<sup>5</sup> Therefore, pre-incisional initiation of analgesia, namely preemptive analgesia, was demonstrated to reduce postoperative pain and the need for rescue analgesics in various investigations.<sup>5,6,31,32</sup> This advantage was even more clear if TEA was used in thoracotomy procedures.<sup>33</sup> Benefits of preemptive TEA on reducing chronic post-thoracotomy pain and modifying immune response were also demonstrated.<sup>5,34</sup> In our study preemptive TEA -provided by continuous infusion of *bupivacaine* for 24 hours- was shown to have a better analgesic effect than our IVA protocol at first 6 hours.

## STUDY LIMITATIONS

The main limitation of this study is the size of the sample population and retrospective nature. Pain assessment was comprehensive and reliable only at postoperative day 0. Hence, the VAS scores of succeeding time intervals could not be included for evaluation. Finally, it might be criticized that proper positioning of the epidural catheter was not verified with an imaging modality.

## CONCLUSION

This study was designed for determining predictors of significant pain at 1<sup>st</sup>, 6<sup>th</sup> and 12<sup>th</sup> hours of postoperative follow-up after lung cancer surgery. Iatrogenic rib fracture and procedure-related complications were associated with significant pain

at 1<sup>st</sup> and 6<sup>th</sup> hours, respectively. Thoracic epidural analgesia was the only consistent determinant of tolerable pain at first 6 hours. Our findings verified the results of various studies addressing the efficacy of TEA on postoperative pain. After 12 hours, none of the variables were related to pain severity.

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#### Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling,

expertise, working conditions, share holding and similar situations in any firm.

#### Authorship Contributions

**Idea/Concept:** Derya Özden Omaygenç, Necati Çıtak, Gamze Babur Güler; **Design:** Derya Özden Omaygenç, Zeynep Nilgün Ulukol, Özgür İşgörücü, İbrahim Celalettin Kocatürk; **Control/Supervision:** Derya Özden Omaygenç, Necati Çıtak, Özgür İşgörücü, Zeynep Nilgün Ulukol, Yunus Aksoy, Cem Emrah Kalafat, Mesut Buz, Çağrı Cemaller; **Data Collection and/or Processing:** Derya Özden Omaygenç, Necati Çıtak, Özgür İşgörücü, Zeynep Nilgün Ulukol, Yunus Aksoy, Cem Emrah Kalafat, Mesut Buz, Çağrı Cemaller; **Analysis and/or Interpretation:** Derya Özden Omaygenç, Gamze Babur Güler, İbrahim Celalettin Kocatürk; **Literature Review:** Derya Özden Omaygenç, Necati Çıtak; **Writing the Article:** Derya Özden Omaygenç; **Critical Review:** İbrahim Celalettin Kocatürk, Gamze Babur Güler; **References and Fundings:** İbrahim Celalettin Kocatürk, Derya Özden Omaygenç.

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