Effects of Preoperatively or Postoperatively Initiated Thoracic Epidural Analgesia in Patients Undergoing Elective Lung Surgery

Elektif Akciğer Cerrahisi Olan Hastalarda Preoperatif veya Postoperatif Başlatılan Torasik Epidural Analjezinin Etkileri

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ABSTRACT Objective: The goal of this study was to investigate the effects of preoperatively and postoperatively initiated thoracic epidural analgesia (TEA) on oxidative stress, respiratory functions and postoperative pain in patients undergoing elective lung surgery. **Material and Methods:** A thoracic epidural catheter was inserted into all the patients before surgery. In Preop- TEA Group (n= 15), bolus dose of 0.175% bupivacaine and 15 μg ml^{-1} fentanyl (0.1 ml kg^{-1}) were administered preoperatively, followed by a continuous infusion of 0.125% bupivacaine and 10 μg ml^{-1} fentanyl combination (0.1 ml kg^{-1} h^{-1}) intraoperatively. In Postop- TEA Group (n= 15), no medication was administered via the epidural catheter preoperatively. Postoperative analgesia was maintained with patient-controlled epidural analgesia (PCA) in both groups for 48 h. We assessed peroperative IV analgesic requirtment and postoperative pain and analgesic consumption, oxidative stress, heart rate, blood pressure, respiratory functions and side effects. The postoperative intensive care unit and hospital stay durations were recorded. Student's t-test, χ^2-test, Mann-Whitney U test, and Wilcoxon's signed rank test were used for group comparisons and statistical conclusions. **Results:** Visual analogue scores were always higher during coughing and at rest, perioperative heart rate was increased in Postop-TEA Group ($p< 0.05$). Total peroperative fentanyl requirement and postoperative analgesic consumption via PCA were lower in Preop- TEA Group ($p< 0.05$). Respiratory function tests were decreased in both groups when compared to the preoperative values ($p< 0.05$), but the differences were small in Preop-TEA group ($p< 0.05$). No marked effect on oxidative stress was determined and shorter length of stay in ICU and hospital shorter in Preop-TEA Group ($p< 0.05$). **Conclusion:** These results suggest that preoperatively initiated TEA provides better postoperative pain relief with improving the outcome and shortening intensive care and hospital stay in patients undergoing elective lung surgery. However, TEA had no marked effect on oxidative stress in our study.

Key Words: Analgesia, epidural; thoracotomy; pain, postoperative; oxidative stress

ÖZET Amaç: Bu çalışmanın amacı elektif akciğer cerrahisi olan hastalarda oksidatif stress, solunum fonksiyonları ve postoperatif ağrı üzerine preoperatif ve postoperatif başlatılan torasik epidural analjezinin (TEA) etkilerini araştırmaktı. **Gereç ve Yöntemler:** Torasik epidural kateter cerrahi öncesi bütün hastalara yerleştirildi. Preop-TEA grubunda, preoperatif bolus doz %0.175 bupivakain ve 15 μg ml^{-1} fentanili (0.1 ml kg^{-1}), intraoperatif 0.125% bupivakaine ve 10 μg ml^{-1} fentanil kombinasyonu (0.1 ml kg^{-1} h^{-1}) ile sürekli infüzyon takip etti. Postop- TEA grubunda epidural kateter yoluyla, hiçbir preoperatif ilaç tedavisi yönetilmedi. Postoperatif analjezi her iki grupta hasta kontrollü epidural analjezi (HKA) ile 48 saat sağlandı. Peroperatif analjezik ihtiyacı, postoperatif ağrı ve analjezik tüketimi, oksidatif stres, kalp hızı, kan basıncı, solunum fonksiyonları ve yan etkileri değerlendirdik. Postoperatif yoğun bakım ve hastanede kalış süreleri kaydedildi. İstatistiksel veriler ve grup karşılaştırmalarında Student's t-testi, χ^2-testi, Mann-Whitney U testi, ve Wilcoxon's signed rank testi kullanıldı. **Bulgular:** Postop- TEA grubunda, vizüel analog skala istirahatte ve öksürme esnasında her zaman daha yüksek, perioperatif kalp atım sayısı daha artmıştı ($p< 0.05$). perioperatif fentanil ihtiyacı ve HKA ile tüketilen postoperative analjezik miktarı Preop- TEA grubunda daha düşüktü ($p< 0.05$). Solunum fonksiyon testleri preoperatif değerler ile karşılaştırıldığında her iki grupta da düşmüştü. Fakat fark Preop- TEA grubunda daha azdı ($p< 0.05$). Preop-TEA grubunda oksidatif stress üzerine belirgin etki saptanmadı, yoğun bakım ve hastanede kalış süresi ise daha kısaydı ($p< 0.05$). **Sonuç:** Bu bulgular, elektif akciğer cerrahisi olan hastalarda preoperatif başlatılan TEA'nın, sonuçları iyileştirmesiyle postoperatif ağrıda daha iyi analjezi sağladığını, hastane ve yoğun bakımda kalış süresini kısalttığını göstermektedir. Fakat çalışmamızda TEA'nın oksidatif stress üzerine belirgin etkisi olmadı.

Anahtar Kelimeler: Analjezi,epidural; torakotomi; ağrı, postoperatif; oksidatif stres

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Thoracotomy is among the most painful operations, and patients can experience severe pain postoperatively. Intercostal nerve damage during surgery induces severe postoperative pain which may be related to development of chronic pain after the thoracotomy.[1,2] A variety of analgesic techniques are used for post-thoracotomy pain control.[1] Thoracic epidural analgesia (TEA) provides optimal perioperative anesthesia and analgesia after thoracic surgery, and decreases postoperative morbidity and mortality.[3] According to several studies, TEA using a local anaesthetic combined with an opioid can be considered as a commonly used standard method in the management of acute post-thoracotomy pain.[4-6] The majority of studies have shown that the use of a local anaesthetic-opioid combination is associated with significantly better dynamic pain relief after thoracic surgery than the components of the mixture infused alone.[3]

The aim of postoperative pain management is to provide good subjective comfort, to contribute early recovery and to have a good outcome after surgery. Effective coughing is necessary for a sufficient bronchial clearance to prevent atelectasis and bronchopulmonary infection. Therefore, many attempts have been made to combine systemic drug administration with different kinds of regional anesthesia to improve postthoracotomy pain control. Severe post-thoracotomy pain puts patients at major risk for pulmonary complications. TEA may also reduce the incidence of chronic post-thoracotomy pain, and may result in earlier recovery of respiratory function after thoracotomy.[5,7,8]

Preemptive analgesia is defined as the concept of decreasing pain perception and overall analgesic need after surgery by use of a drug regimen capable of inhibiting central nervous system sensitization before the application of painful stimuli.[9] By decreasing the altered central sensory processing, preemptive analgesia is thought to consequently block the painful stimuli after surgery.[9,10] S recent meta-analysis reported that preemptive analgesia showed an overall beneficial effect in selected analgesic regimens that was most pronounced after epidural analgesia.[10,11] Since the validity and clinical relevance of preemptive analgesia has been questioned and stated that any effects of preemptive analgesia may not translate into clinically relevant longterm improvements in patient satisfaction or outcome,[12-14] the objective of the present study was to evaluate the contribution of preoperatively initiated TEA on thoracic epidural pain relief after elective lung surgery. Although it has been suggested that oxidative stress may occur following pulmonary resection,[15] changes in plasma and bronchoalveolar lipid peroxidation and nitric oxide (NO) levels are not studied in patients undergoning lung surgery. It can be hypothesised that the timing of epidural analgesia might be expected to alter plasma or bronchoalveolar lavage (BAL) levels of malondialdehyde (MDA) or NO. Therefore, examining the effects of anesthesia and thoracic surgery on plasma and bronchoalveolar MDA and NO levels was also aimed in this study.

MATERIAL AND METHODS

The study protocol was approved by the medical ethics committee of our faculty and a written informed consent was obtained from each patient. Thirty consenting American Society of Anaesthesiologists (ASA) physical status I-III patients undergoing posterolateral midthoracic incision without costectomy were randomly divided into two groups to evaluate the effects of two different analgesia techniques Group I (n= 15): Postop-TEA (Control group) and Group II (n= 15): Preop-TEA. Exclusion criteria were ASA physical status more than III, age older than 80 yr or younger than 18 yr, severe cardiac disease, body mass index more than 30 kg m^{-2}, history of allergy to local anesthetics or opioids, current opioid use, endocrine, metabolic or central nervous system disorders, active infectious process, neurological disorders, abnormal coagulation tests, renal or hepatic failure, lack of cooperation, or inability to comprehend or perform verbal and physical assessments. On the day before surgery, patients received instructions on how to use a patient-controlled epidural analgesia (PCEA) device (Abbott Pain Management Provider, Donegal, Ireland), and measure pain with a visual analog scale (VAS) that consisted of an unmarked 10-cm line, with 0 cm representing no pain and 10

cm representing the worst pain imaginable. Postoperative pain methodology during the 48 h period was explained to all patients.

After arrival into the operating room, all the patients were premedicated with midazolam 3 mg IV and were given 10 mL kg^{-1} h^{-1} ringer's lactate solution, and received 2 L min^{-1} oxygen with a nasal catheter. Patients were monitored (Nihon-Kohden BSM-4113K, Japan) with electrocardiography, pulse oximetry and non-invasive blood pressure measurements.

Preoperatively, an 18 G epidural catheter (Portex® Epidural Minipack, Hythe, UK) was inserted into all patients, through the T4-T5 or T5-T6 intervertebral space by a midline approach with the loss of resistance technique, and it was placed 4–5 cm in the cephalad direction. After a negative aspiration test, a test dose of 3 ml 2% lidocaine (Jetokain Simplex, Adeka, Samsun, Turkey) was injected into the catheter to exclude subarachnoid placement.

In this prospective randomized study, patients were allocated to group 1 or group 2 using a computer-generated table of pseudo-random numbers. In the Preop- TEA Group, an epidural bolus dose of 0.175% bupivacaine and 15 μg ml^{-1} fentanyl (0.1 ml kg^{-1}) was administered during surgical preparation and draping which followed by a continuous infusion of 0.125% bupivacaine and 10 μg ml^{-1} fentanyl combination (0.1 ml kg^{-1} h^{-1}) until admission to the intensive care unit (ICU). In postop-TEA Group, no epidural medication was applied until the chest closure. At skin closure, a bolus dose of 0.175% bupivacaine and 15 μg ml^{-1} fentanyl (0.1 ml kg^{-1}) was applied via the epidural catheter to the patients in postop-TEA group. Patients were blinded to the groups.

In the ICU, postoperative analgesic treatment was similar and obtained with PCEA in both groups. PCEA was administered during postoperative period with 0.1% bupivacaine plus 5 μg ml^{-1} fentanyl combinations according to the following program: No initial dose, basal infusion rate 0.1 ml kg^{-1} h^{-1},[16] bolus dose 4 ml and 15 min lock out interval. No changes were made to the PCEA setting. No background infusion was permitted.

General anesthesia was induced with 2 μg kg^{-1} fentanyl, 2 mg kg^{-1} propofol and 0.1 mg kg^{-1} vecuronium, and maintained with 1-4% sevofluane in O_2/air mixture. The concentration of sevoflurane was adjusted to changes in blood pressure and heart rate. Postop-TEA Group was control group and the patients received only general anesthesia (2-4% sevoflurane). The patients in preop-TEA group received light general anesthesia (1-2% sevoflurane) plus thoracic epidural analgesia (bupivacaine + fentanyl). A left-sided double-lumen tube for one-lung ventilation, a subclavian catheter for central venous pressure monitoring, a radial artery catheter for invasive blood pressure monitoring and blood gas analysis, and an indwelling bladder catheter to determine the intraoperative urine output were inserted. The correct position of the endobronchial tube was confirmed by fiberoptic bronchoscopy after the patient was in the lateral decubitus position. Hypotension was treated with incremental doses of IV ephedrine (5 mg). Further muscle relaxation with vecuronium was administered at the discretion of the anesthesia team. Whenever the blood pressure or heart rate increased by more than 20%, depth of anesthesia was judged inadequate, and hemodynamic control was ensured with incremental doses of IV fentanyl (100 μg). The same surgeon (AS) who was not aware of the patient's assignment performed all the operations. Patients were awakened and their tracheas were extubated at the conclusion of surgery when they met standard extubation criteria (SpO_2 >90% while inspired O_2 fraction (FIO_2) ≤ 0.40, negative inspiratory force > -20 cmH_2O, vital capacity > 15 $ml.kg^{-1}$) . The patients were transferred to the ICU for close monitoring over the next 48 h. Patients were then transferred to the service when their arterial blood SpO_2 ≥95%, PO_2 >80 mmHg, PCO_2 35-45 mmHg values were obtained. When the patient's hemodynamic parameters were stable with no fever, and following the removal of the drains and tubes, patients were discharged from the hospital.

Perioperative parameters [systolic artery pressure (SAP), diastolic artery pressure (DAP), mean arterial pressure (MAP), heart rate (HR), SpO_2 and

end tidal CO_2] were measured and recorded during induction, incision, and at 5, 10, 15, 30 and 60 min after induction. Perioperative IV analgesic requirement and sevoflurane consumption (by weighing the vaporizer)[17] were recorded. VAS assessments, $PaCO_2$, HR, SAP, DAP, MAP, respiratory rate and side effects were assessed at postoperative 1, 2, 4, 8, 12, 16, 20, 24, 36 and 48 h. Bedside pulmonary function tests [forced vital capacity (FVC), forced expiratory volume in 1 sec (FEV1), and peak expiratory flow (PEF) rate] were performed preoperatively (baseline) and 72 h after surgery.

During the first 48 h after the operation, patients used the epidural PCA as described in the protocol and they were questioned about their pain at 1, 2, 4, 8, 12, 16, 20, 24, 36 and 48 h at rest and coughing by an observer blinded to treatment groups using VAS and the results were recorded. The total amount of analgesics the patient received and the number of requests for analgesia from the pump were recorded.

The degree of sedation was also examined by the same observer on a five-point scale (0= alert, 1= mildly drowsy, 2= moderately drowsy, easily rousable, 3= very drowsy, rousable, 4= difficult to rouse or 5= unrousable). Side effects, including nausea, vomiting, hypertension (diastolic arterial blood pressure > 100 mmHg), hypotension (mean arterial pressure < 60 mmHg), bradycardia (with hypotension, heart rate < 45), sedation, hypoventilation (SpO_2 <90), and pruritus were recorded and treated with appropriate medications. The postoperative intensive care unit and hospital stay durations were recorded.

NO and MDA levels were measured in a blind manner in plasma, and BAL samples were collected following induction of anesthesia and at the 150th. min of surgical operation. We instilled 10-ml normal saline through aspirator tube, aspirated 20-ml BAL specimen immediately and took it into the tube. We kept the specimens in the refrigerator for 30 minutes. Both plasma and BAL NO levels were measured by a NO/ozone chemiluminescence technique published by Goksu et al.[18] The concentrations of NO metabolites in the samples were determined by comparing with the standard curve and expressed as μM. MDA levels as an indication of lipid peroxidation were measured using the thiobarbituric acid reaction according to methods described by Buege and Aust.[19]

All data are expressed as mean ± standard deviation unless stated otherwise. Statistical analysis was carried out using the unpaired student's t-test for SAP, DAP, MAP and HR differences between groups. c^2-test was used for nausea, vomiting and other adverse events. VAS scores and number of postoperative PCA requests were analyzed with a Mann-Whitney U test. Wilcoxon's signed rank test was used for repeated measurements. $P< 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS version 11.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

Demographic characteristics of patients in both groups and type of surgery are shown in Table 1. Demographic data were similar in two groups. There were no marked differences in hemodynamic parameters between groups before the anesthesia induction. Although there were no marked changes in mean arterial blood pressure, marked increases in heart rate in Postop- TEA Group but not in Preop-

TABLE 1: Patient characteristics.

	Group 1 (n= 15)	Group 2 (n= 15)	P
Age (yr)	41 ± 15	46 ± 14	0.35
Gender (F/M)	6/9	4/11	0.70
Height (cm)	166 ± 8	171 ± 6	0.06
Weight (kg)	70 ± 13	69 ± 14	0.84
ASA (I / II/III)	3/8/4	2/8/5	0.86
Operation			
■ lobectomy	3	5	
■ pneumonectomy	2	3	
■ cystotomy ± capitonnage	3	2	
■ others	7	5	
■ Wedge resection	2	2	
■ Pleural decortication	3	2	
■ Bullectomy	2	1	

Data are given as mean ± SD or numbers of patients. Group I; Postop-TEA (thoracic epidural anesthesia) (Control group), Group II; Preop-TEA.
ASA: American Society of Anesthesiologists physical status.

TEA Group were recorded peroperatively (Figures 1, 2). No patient was receiving ephedrine, beta-adrenergic blocking or antihypertensive drugs.

Durations of operations were 182.93 ± 31.62 min and 208.26 ± 38.27 min in the Postop- TEA Group and Preop- TEA Group, respectively. Duration of anesthesia was not markedly different in two groups (186.73 ± 33.07 min for Postop-TEA Group and 212.33 ± 32.65 min for Preop-TEA Group, P> 0.05).

In both groups, the values of forced vital capacity (FVC), forced expiratory volume in 1 sec (FEV_1) and peak expiratory flow rate (PEF,%) on the day 3 were significantly lower when compared to the preoperative values. These differences were markedly lower in Preop-TEA Group (P< 0.05, Figure 3).

The amounts of sevoflurane consumption were 210.33 ± 34.92 g and 179.66 ± 38.47 g in Postop- TEA Group and Preop- TEA Group, respectively (P< 0.05). Perioperative IV fentanyl requirement and postoperative total analgesic consumption were also lower in Preop- TEA Group when compared to Postop- TEA Group (P< 0.05, Table 2). Two different pain indicators were used: VAS (at rest and while coughing) and number of PCA requests. As seen in Figures 4 and 5, both VAS values during coughing and at rest decreased through the first 48 h postoperatively in both groups.

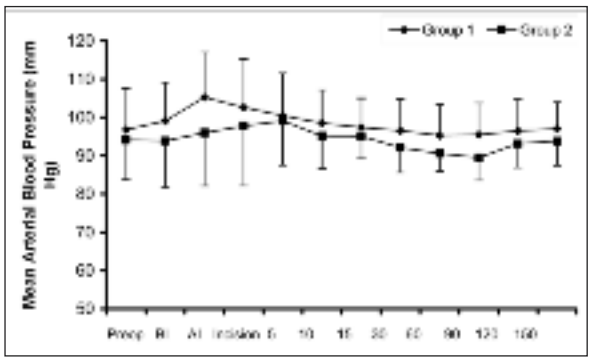

FIGURE 1: Effects of general anesthesia and general anesthesia + thoracic epidural analgesia with bupivacaine and fentanyl on mean arterial blood pressure in patients underwent elective lung surgery.

Preop, preoperation; BI, before induction; AI, after induction. Values are given as mean ± S.D. Group I; Postop -TEA (thoracic epidural anesthesia) (Control group), Group II; Preop-TEA. *P< 0.05 when compared to group 2.

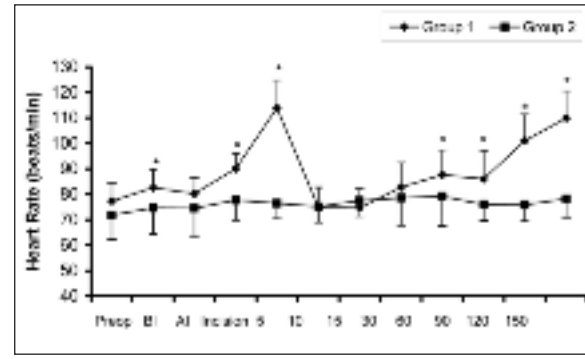

FIGURE 2: Effects of general anesthesia and general anesthesia + thoracic epidural analgesia with bupivacaine and fentanyl on heart rate in patients underwnet elective lung surgery.

Preop, preoperation; BI, before induction; AI, after induction. Values are given as mean ± S.D. Group I; Postop -TEA (thoracic epidural anesthesia) (Control group), Group II; Preop –TEA. *P < 0.05 when compared to group 2.

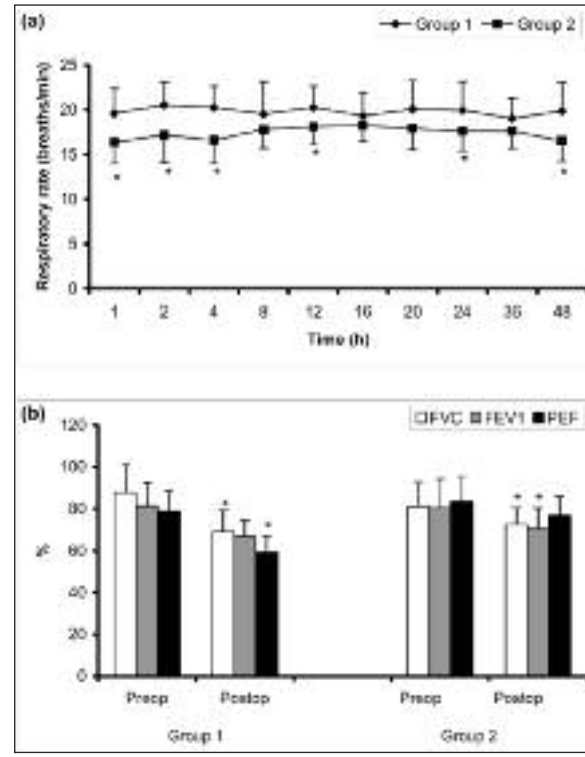

FIGURE 3: Effects of general anesthesia and general anesthesia + thoracic epidural analgesia (bupivacaine + fentanyl) on postoperative respiratory rate (a) and respiratory function tests (preoperation and postoperation at day 3) (b) in patients undergoing elective lung surgery.

Preop, preoperation; Postop, postoperation. FVC, forced vital capacity; FEV1, forced expiratuar volume at first sec; PEF, peak expiratuar flow. Group I; Postop-TEA (Control group), Group II; Preop-TEA. *P< 0.05 when compared to group 1 (a) and preoparation values (b).

Postoperative VAS values during coughing in the first 12 h and in rest at the first 20 h were markedly lower in Preop- TEA Group than Postop- TEA

TABLE 2: Peroperative IV fentanyl requirement, postoperative total analgesic consumption and number of postoperative PCA requests.

	n	Peroperative IV fentanyl consumption (≒g)	Postoperative total analgesic consumption via PCA (ml)	Number of postoperative PCA requests+
Group 1	15	253.33 ± 48.05	286.66 ± 34.36	63 (50-78)
Group 2	15	143.33 ± 37.16*	205.66 ± 32.45*	41 (35-56)*

PCA: patient controlled analgesia; + Presented as median (min-max).

Group I; Postop -TEA (thoracic epidural anesthesia) (Control group), Group II; Preop –TEA. *P < 0.05 when compared to group 1.

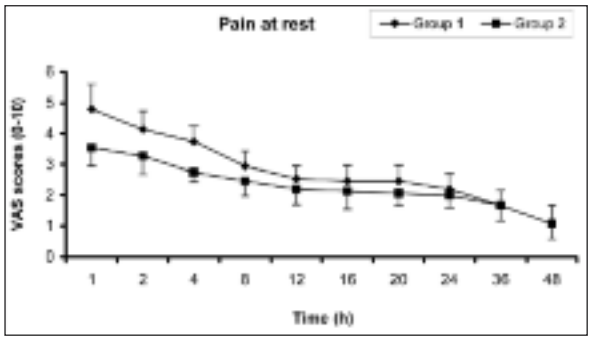

FIGURE 4: Effects of general anesthesia and general anesthesia + thoracic epidural analgesia (bupivacaine + fentanyl) on VAS scores during at rest in patients underwent elective lung surgery.

Group I; Postop -TEA (thoracic epidural anesthesia) (Control group), Group II; Preop –TEA. *P< 0.05 when compared to group 1.

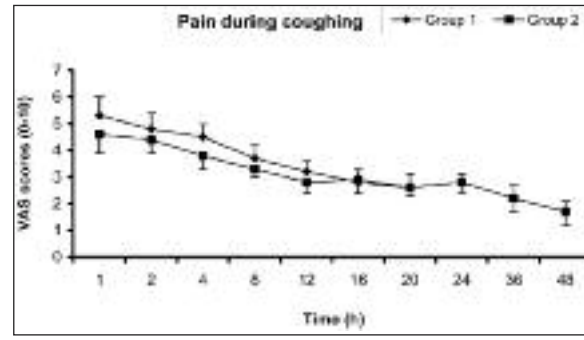

FIGURE 5: Effects of general anesthesia and general anesthesia + thoracic epidural analgesia (bupivacaine + fentanyl) on VAS scores during coughing in patients underwent elective lung surgery.

Group I; Postop -TEA (thoracic epidural anesthesia) (Control group), Group II; Preop –TEA. *P < 0.05 when compared to group 1.

Group (P< 0.05, Figure 4, 5). Number of PCA requests was significantly diminished in Preop- TEA Group (P< 0.05, Table 2). Better pain relief was achieved with preoperatively initiated TEA.

There were no episodes of hypotension, bradycardia, or hypoventilation. During postopretive period, SAP, DAP, MAP, HR, SpO_2 and $ETCO_2$ values did not change markedly. No significant changes were found in oxygen saturation levels of the two groups (P> 0.05, data not shown). Postoperative nausea, vomiting, pruritus and sedation scores were not significantly different between the groups. There were no severely sedated patients in any group (no patient was mostly sleeping), and no case of respiratory depression was observed. No neurological sequelae caused by thoracic epidural catheterization were seen in the early postoperative period.

Plasma MDA levels were markedly increased at the 150th. minutes of operation in both groups (Figure 6). This increase was accompanied by a significant decrease in plasma NO levels (Figure 7). In

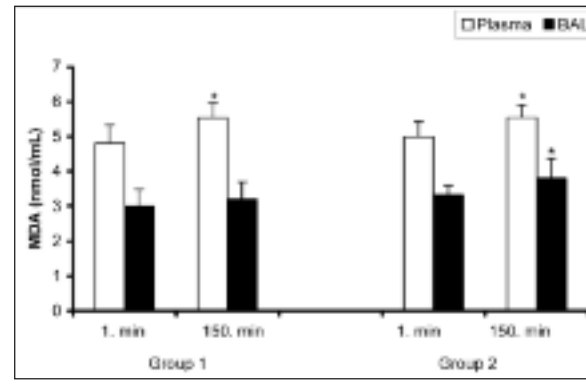

FIGURE 6: Effects of general anesthesia and general anesthesia + thoracic epidural analgesia (bupivacaine + fentanyl) on plasma MDA in patients underwentg elective lung surgery.

Values are given as mean ± S.D. Group I; Postop-TEA (thoracic epidural anesthesia) (Control group), Group II; Preop-TEA. *P< 0.05 when compared to first min values.

Preop- TEA Group, bronchoalveolar MDA levels were also markedly augmented.

The time of stay in the postoperative intensive care unit (2.6 days for Postop-TEA Group vs. 2.1 days for Preop-TEA Group, P< 0.05) and in the

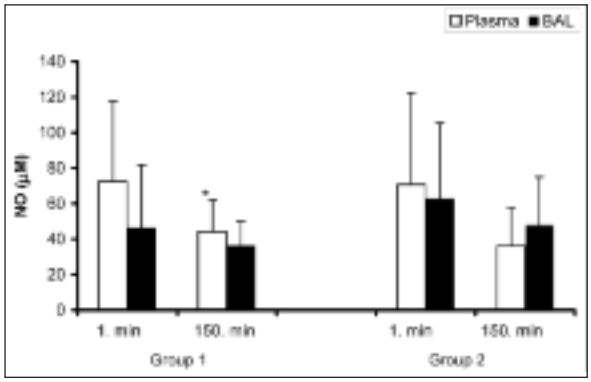

FIGURE 7: Effects of general anesthesia and general anesthesia + thoracic epidural analgesia (bupivacaine + fentanyl) on plasma nitric oxide (NO) levels in patients underwent elective lung surgery.

Values are given as mean ± S.D. Group I; Postop -TEA (thoracic epidural anesthesia) (Control group), Group II; Preop –TEA. *P< 0.05 when compared to first min values.

hospital (7.5 days for Postop-TEA Group vs. 6.6 days for Preop-TEA Group, P< 0.05) were markedly reduced in Preop-TEA Group.

DISCUSSION

Our study demonstrated that preemptive analgesia was associated with a better control of acute postoperative pain, with less need of supplemental IV and epidural medications, less reduction in the forced expiratory variables, shorter length of stay in the ICU and early discharge from the hospital without any difference in undesired side effects. Our findings are supported by the previous observations reporting that epidural analgesia has the potential to reduce or eliminate the perioperative physiologic stress responses to surgery and thereby decrease surgical complications and improves outcomes.[20,21] TEA is considered as a gold standard after major thoracic surgery. It has been concluded in a recent review that thoracic epidural analgesia was superior to intrathecal and intercostal techniques, and either thoracic epidural analgesia with local anesthetic plus opioid or continuous paravertebral block with local anesthetic can be recommended for post-thoracotomy analgesia.[22] The synergistic effect of local anaesthetic and opioid combination is well known and it provides better analgesia during activity. Epidural analgesia with opioids, especially fentanyl, in combination with bupivacaine is widely used. The rationale for such a combination is a putative additive or synergistic effect which will provide effective analgesia with reduced doses, and therefore reduced side effects of both drugs.[23,24] One of the main advantages of the preoperatively initiated TEA was the stability of cardiovascular parameters. There were no marked changes in mean arterial blood pressure or heart rate in postop-TEA group in our study.

Preemptive epidural analgesia proved effective in reducing supplemental analgesic consumption. This was in accordance with a previous study in which it was demonstrated that the total dose of local anaesthetic determined the quality of analgesia.[25] Preoperative epidural analgesic treatment is more effective in managing acute postoperative pain, attenuating pain scores, and decreasing the total supplemental analgesic consumption. Therefore, our results support the conclusion that preemptive epidural analgesia is effective and clinically useful in reducing postoperative pain intensity scores.

The bupivacaine-fentanyl combination produced good intra-operative and post-operative analgesia and shorter duration of stay in critical care unit and in hospital. Our data are not in agreement with the studies reporting no advantage of these drugs in combination following thoracotomy.[12,26] In these studies that Ochroch et al. administered 6 ml of a mixture of 0.375% bupivacaine and 3 μg ml^{-1} of fentanyl citrate followed by an infusion of the same mixture at a rate of 8 ml h^{-1}.[26] Drugs were administered intraoperatively through the epidural catheter. Aguilar et al. used 0.5% bupivacain with adrenalin 5 μg ml^{-1} in a total volume of 8 ml in preemptif TEA.[12] The fentanyl dose (15 μg ml^{-1}) was higher in our study. Our results support the conclusion that the combination of opioid and local anaesthetic infusion via thoracic epidural catheter following thoracic surgery can be considered as one of the very effective methods for relieving postthoracotomy pain. TEA with local anesthetic can improve pulmonary outcomes by attenuating the physiologic response to surgery, controlling postoperative pain, permitting earlier extubation, and reducing length of stay.[14,15,22,23]

TEA that covers the whole perioperative period in addition to the postoperative phase has been shown to be significantly better than the postoperative TEA and IV-PCA.[27] Postoperative PCA provides high quality of analgesia and it is possible to titrate the doses of analgesics. Peroperative IV fentanyl requirement and postoperative total analgesic consumption were found to be lower in general anesthesia plus TEA group in our study. Liu et al. similarly showed that PCA decreased epidural bupivacaine/fentanyl requirements and improved analgesia and patient satisfaction.[4] A shorter length of stay in the ICU and early discharge from the hospital has been observed in Preop-TEA Group, this may be an important outcome of this study in terms of economy.

Similar to our study, Yegin et al. showed that preoperative TEA combined with the postoperative PCA was an appropriate and effective method for the reduction of early postthoracotomy pain, and the use of bupivacaine plus fentanyl for both types of epidural analgesia was safe and effective.[28] Neustein et al. demonstrated that while there was a beneficial effect of reduced intraoperative anesthetic requirements, any lasting effect of preemptive analgesia did not extend beyond six hours after the operation.[23] We also found that postoperative VAS values were markedly reduced in patients receiving epidural analgesia. Our findings support the conlusion that the preoperative administration of bupivacaine plus fentanyl has a marked pre-emptive effect and significantly reduces post-thoracotomy pain in the first 20 h.

There was an approximately 20% reduction in the forced expiratory variables (FVC1, FEV1, and PEF) on the third postoperative day in patient received sevoflurane anesthesia. However, sevoflurane anesthesia with TEA produced less reduction in FVC1 and FEV1 (approximately 10%). Additionally, there were no differences in PEF values between the preoperative and postoperative period in sevoflurane anesthesia in TEA group. Thoracic epidural analgesia can increase PaO_2 and reduce the incidence of postoperative atelectasis, pneumonia, and hypoxemia.[29]

There was a marked decline in plasma NO levels with lung sugery in our study. The significantly reduced level of NO plasma levels following surgical trauma is also in accordance with the results of other investigators[30,31] and different injury-mediated events could account for the circulating NO decrease in the postoperative phase. A significant decrease of plasma NO levels at the end of surgery has been reported and this reduction remained at 24h postoperatively.[31] Plasma levels of NO have been found to be impaired in the early postoperative period.[30] In the current study, we found that the plasma and BAL NO levels was unaffected by the anesthesia regimen, as patients who received TEA plus general anesthesia exhibited similar changes in NO levels. Thus, these results could suggest that in patients undergoing an elective lung surgery, the decrease of NO plasma and BAL concentration is due a great extent to the surgical stress. Sevoflurane, at a clinically attainable concentration, has been reported to significantly increase intracellular free radials and NO release from human polymorphonuclear (PMN) leukocytes.[32] However, fentanyl does not have the ability to influence NO release from human endothelial cells and has no influence on neutrophil function.[33,34] As a result, it also lacks the ability to downregulate the inflammatory response associated with surgery. Low levels of NO during surgery may also suggest that NO is consumed with the combination of superoxide to form peroxynitrite which induces oxidative stress such as lipid peroxidation, and as a consequence, causes cell damage.[35]

Our data showed that there were marked elevations in plasma and BAL MDA levels. Increased exhaled H_2O_2 concentrations in breath condensate and MDA levels in urine samples have been shown in patients with lung carcinoma undergoing thoracotomy.[15] These findings suggest that oxidative stress may occur following lung surgery. Changes in several markers of oxidative stress following lung resection have been demonstrated in another study.[36] It has been reported that epidural anesthesia with bupivacaine may attenuate lipid peroxidation in patients undergoing aorto-femoral

bypass grafting.[37] Bupivacaine is able to scavenge free radicals and inhibit PMN leukocyte free radical release at high concentrations, therefore it is likely that bupivacaine at therapeutic concentrations does not suppress leukocyte function in vivo.[38] A clinical report demonstrated that plasma MDA levels significantly increased after sevoflurane induction at the end of surgery suggesting that sevoflurane might cause lipid peroxidation during laparoscopic cholecystectomy.[39] Sevoflurane can also directly trigger the peroxynitrite formation.[40] Thus, the increased MDA and decreased NO levels may be physiologically important indicators of oxidative stress in lung surgery.

In conclusion, the present study revealed that preoperatively initiated TEA proved to be beneficial and effective for the control of the post-thoracotomy pain, with the advantages of decreasing general anaesthetic consumption and reducing time of to hospitalization. Our results suggest that combined general anesthesia and epidural analgesia is better than general anesthesia alone in the patients undergoing thoracic surgery. TEA with preoperative initiation is a preferable method for preventing acute thoracotomy pain. Our data also imply that oxidative stress markedly increased with surgery, and this increase is not modified with the use of analgesic drugs.

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