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Effects of epidural morphine and levobupivacaine combination before incision and after incision and in the postoperative period on thoracotomy pain and stress response

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Background/aim: This study aims to investigate the effects of thoracic epidural analgesia, before and after surgical incision and in the postoperative period, on thoracotomy pain and stress response.

Materials and methods: A total of 45 patients who were scheduled for posterolateral thoracotomy were included in this study. A combination of epidural levobupivacaine and morphine was administered as a bolus before incision (Group 1; n=15), after incision (Group 2; n=15), or at the end of surgery (Group 3; n=15). Additionally, infusion was used in Group 1 and Group 2 during operation. Postoperative patient-controlled epidural analgesia infusion pumps were connected to all patients. Visual analog scale (VAS) scores and morphine consumption were recorded during the postoperative 48 h. Glucose, insulin, cortisol, and C-reactive protein (CRP) levels were compared before surgery and at 4, 24, and 48 h after the operation.

Results: There were no differences in the morphine consumption and VAS scores for all measurements among the groups ($P > 0.05$). Both blood glucose levels at 4 h and CRP values at 48 h were higher in Group 2 than Group 1 ($P < 0.05$). Cortisol levels at 4, 24, and 48 h after the operation were similar to baseline values in all groups ($P > 0.05$).

Conclusion: The application of thoracic epidural analgesia before and after surgical incision and in the postoperative period did not result in a significant difference in the severity of the postthoracotomy pain and stress response in all groups. Based on our results, we suggest that epidural levobupivacaine combined with morphine provides an effective and safe analgesia and can partially suppress surgical stress response.

Key words: Epidural analgesia, thoracotomy, pain, analgesic consumption, preemptive analgesia, stress response

1. Introduction

Postthoracotomy pain is one of the most painful postoperative pain types. Early and effective postthoracotomy pain management provides improved pulmonary functions and reduces the complication rates (1,2). Inadequate postthoracotomy analgesia results in decreased normal and deep breathing, ineffective coughing, retention of bronchial secretions, atelectasis, and acute restrictive pulmonary disease (2).

Postthoracotomy analgesic treatment regimens include narcotics, nonsteroid antiinflammatory drugs, and transcutaneous nerve stimulation or regional interventions such as intercostal, intrapleural, and paravertebral block or epidural block (3,4).

Today, thoracic epidural analgesia is accepted as the gold standard in postthoracotomy pain treatment (1). Postoperative pain, originating from tissue damage due to surgical trauma, is a type of nociceptive pain accompanied by central and peripheral sensitization. Pain treatment should start before or during dysfunction processes caused by pain. Preemptive analgesia means avoiding pain by initiating the treatment before trauma or surgery (3–5).

It has been known that the prevention of the release of inflammatory mediators using preemptive methods suppresses the stimulation of pain receptors and increases the pain threshold. Preventive analgesia is described as a course that starts in the preoperative period and continues throughout the postoperative period. It should be accepted as a method of pathological pain treatment rather than a conventional perioperative strategy for physiological pain (6,7). Postoperative pain control provides not only analgesia, but also reduction of surgical stress response and

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prevention of neuroendocrine stimulation. The effective blockage of the sympathoadrenal system, suppression of the cortisol response, and early mobilization are critical in patients with cardiovascular and pulmonary diseases (8–10).

Preemptive continuous epidural treatment extending into the postoperative period might reduce nociceptive input caused not only by incision and ongoing surgery, but also by postsurgical inflammation (11). It has been investigated in what time period analgesic agents should be applied to provide effective analgesia and to prevent surgical stress responses. In the present study, we aimed to investigate the effects of thoracic epidural morphine and levobupivacaine combination administered before the incision, after the incision, or in the postoperative period in patients undergoing thoracotomy.

We evaluated the amounts of analgesics that were consumed during epidural patient-controlled analgesia (PCA) primarily. The secondary aim was to observe effects on thoracotomy pain, surgical stress response, and hemodynamic status.

2. Materials and methods

The study was approved by the Institutional Ethics Committee and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from each patient.

A total of 45 patients (19 females and 26 males) who underwent elective thoracotomy were included in this study. Patients who had endocrine disease, coronary artery disease, congestive heart failure, psychiatric disease, drug addiction, allergies to local anesthetics and opioids, or contraindication for the placement of epidural catheters were excluded from the study.

All patients were aged between 18 and 66 years with a class of II–III according to the American Society of Anesthesiology. The patients were randomly assigned to three groups including 15 patients in each. The sealed envelope method was used for randomization.

The patients were informed about the visual analog scale (VAS) to evaluate postoperative pain. The VAS scores during resting (VASr) and coughing (VASc) were obtained. We used a 10-cm ruler to evaluate the pain severity, where 0 indicates no pain and 10 indicates intolerable pain.

The mean arterial blood pressure (MABP), heart rate (HR), respiratory rate (RR), and peripheral oxygen saturation (SpO_2) were recorded for all patients in the premedication room. Midazolam (0.07 mg/kg) and atropine (0.01 mg/kg) were injected intramuscularly (i.m.) for premedication 30 min before the surgery. A peripheral vein catheter was placed and 500 mL of crystalloid infusion was started. An epidural catheter was inserted in the sitting position using aseptic techniques. First, prilocaine (2%, 60 mg) was injected for local anesthesia. An epidural catheter was inserted to the midline of the spinous processes between either T 6-7 or T 7-8 using the hanging drop technique with an 18-G Tuohy needle. The catheter was inserted 5 cm into the epidural space and secured to the skin. A test dose of 1% of 3 mL of lidocaine was applied. About 15 min later, motor blockage was assessed using the Bromage scale. According to the scale, patients without motor blockage were moved to the operation room. All patients were operated on under general anesthesia. Propofol (2 mg/kg), fentanyl (1–1.5 μg/kg), and vecuronium bromide (0.1 mg/kg) were given intravenously (i.v.) for anesthesia induction. Anesthesia was maintained using 100% O_2 and 1%–2% sevoflurane during one-lung ventilation and 50% O_2 + 50% air and 1%–2% sevoflurane during two-lung ventilation.

A total of 25 to 100 μg fentanyl was administered i.v. to the patients with elevated HR (by 30%) and MABP (by 20%) compared to the baseline values. No other analgesic agent was used. At the end of the operation, the neuromuscular blockage was antagonized using 0.03 mg/kg i.v. neostigmine and 0.5 mg i.v. atropine sulfate. After the patients were extubated, they were admitted to the surgical intensive care unit (ICU).

A levobupivacaine (2.5 mg/mL) and morphine (0.2 mg/mL) combination was prepared in 10 mL of 0.9% NaCl as a bolus dose. The same bolus dose was applied to all groups. The patients in the preoperative thoracal epidural analgesia group (Group 1) received the bolus injection 30 min before the surgical incision and the intraoperative thoracal epidural analgesia group (Group 2) received it 30 min after the surgical incision. The bolus dose was administered in the postoperative thoracal epidural analgesia group (Group 3) at the end of the operation. A combination of 1.25 mg/mL levobupivacaine and 0.1 mg/mL morphine was prepared in 0.9% NaCl (25 mL of 0.5% levobupivacaine and 74 mL of 0.9% NaCl and 1 mL (10 mg) morphine) for Group 1 and Group 2. The infusion was initiated immediately after the bolus injection at a rate of 5 mL/h and continued until the end of the operation in these groups. In the ICU, this solution was applied via epidural PCA to all groups. A basal infusion rate of 5 mL/h, loading dose of 5 mL, delivery bolus dose of 2 mL, and 20 min of lock-out time were administered in the epidural PCA.

If the MABP decreased 30% or more, crystalloid was infused i.v.. If there was no response, ephedrine (5 mg) was given i.v.. Atropine (0.5 mg) was also infused i.v. for patients with HR lower than 50/min. In the case of nausea and vomiting, metoclopramide was administered i.v. In patients with shoulder pain and a VASc score of ≥4, we administered 75 mg of diclofenac sodium (i.m.).

To evaluate the surgical stress response, we collected blood samples before surgery and at the postoperative

4th, 24th, and 48th hours. Glucose, cortisol, insulin, and C-reactive protein (CRP) levels were measured. The cortisol and insulin levels were measured using an electrochemiluminescence immunoassay (Roche Modular EVO E-170 Hormone Autoanalyzer).

The MABP, HR, SpO_2, VASr, VASc, sedation scores, and motor blockage scores were recorded at baseline (no bolus of local anesthetic and morphine was applied), before the surgical incision, 30 min after the incision, at the end of surgery, and at the time of admission to the ICU (without PCA) at the 1st, 2nd, 4th, 6th, 12th, 24th, and 48th hours after PCA. The Ramsay Sedation Scale was used to evaluate the sedation level (1: anxious, agitated, restless; 2: cooperative, oriented, tranquil; 3: responsive to commands only, prone to sleep; 4: the patient is sleeping, but he/she responds quickly to light glabellar tap or loud auditory stimulus; 5: the patient is sleeping, but he/she responds slowly to light glabellar tap or loud auditory stimulus; 6: no response to light glabellar tap or loud auditory stimulus). In addition, PCA delivery doses and complications were recorded in all of the study periods. Side effects such as respiratory depression, nausea, vomiting, hypotension, bradycardia, itching, shoulder pain, urinary retention, and constipation were assessed during the postoperative 48 h. Metoclopramide i.v. was administered for nausea and vomiting. Respiratory depression was defined as RR less than 10/min and SpO_2 less than 90%. In patients in whom hypotension was unable to be managed with crystalloids and colloids, we administered ephedrine i.v. In the case of bradycardia, 0.5 mg of atropine was injected. After the postoperative 48 h, the routine analgesia protocol adopted by the clinic was applied.

2.1. Statistical analysis

Statistical analysis was performed using SPSS 11.5 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed as mean ± standard deviation (SD) or median (min–max). Categorical data were evaluated using either the chi-square test or Fisher's exact test. One-way analysis of variance (ANOVA) was used to evaluate parametric data, while the Kruskal–Wallis test was used for nonparametric data. For intragroup analyses, repeated measures ANOVA was used for parametric data and Friedman's test was used for nonparametric data. In a previous study (12), the response within each subject group was normally distributed with SD of 9.7. The true difference in the experimental and control means was 16.2 according to analgesic requirement with epidural PCA. We needed to study 7 experimental subjects and 7 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups were equal with probability (power) of 80%. The type I error probability associated with this test of this null hypothesis is 0.05.

3. Results

There were no statistically significant differences in the demographic data among the three groups. Type and duration of surgery were also similar among the groups ($P > 0.05$, Table 1).

The MABP values were only significantly lower at the postoperative 4th and 48th hours in Group 1 compared to Group 2 ($P < 0.05$). In addition, there were no significant differences in the HR among the groups ($P > 0.05$). Group 3 had significantly higher RR values (23.6 ± 2.4) at postoperative 2nd hour compared to Group 1 (20.73 ± 3.4) ($P < 0.05$). In addition, none of the patients had respiratory depression. At all time points, SpO_2 values were similar among the groups ($P > 0.05$), and SpO_2 values did not decrease below 90% in any group.

The delivery doses of the PCA pump were compared among the groups, and no significant difference was found ($P > 0.05$). Total PCA morphine consumption was also similar ($P > 0.05$, Table 2). The Ramsay Sedation Scale scores were also similar among the groups ($P > 0.05$).

Furthermore, both VASr and VASc values were similar among the groups before PCA and during the postoperative 48 h (Tables 3 and 4) ($P > 0.05$).

In addition, there were no differences among the groups in terms of intraoperative fentanyl i.v. and postoperative additional analgesic requirements ($P > 0.05$). However, blood glucose levels at the postoperative 4th hour were significantly higher in Group 2 than Group 1 ($P < 0.05$, Table 5). Blood glucose levels at the postoperative 4th, 24th, and 48th hours in the three groups were also higher than the baseline blood glucose levels ($P < 0.05$).

On the other hand, there were no significant differences in insulin values at baseline and the postoperative 48th hour among the groups ($P > 0.05$, Table 6). Compared to baseline values, Group 1 and Group 2 had higher insulin values at the postoperative 48th hour, while Group 3 had higher insulin values at the postoperative 24th and 48th hours ($P < 0.05$).

Cortisol values were found to be similar among the groups, including the pre- and postoperative 48th hours, at the same time points ($P > 0.05$, Table 7). Cortisol values at the postoperative 4th, 24th, and 48th hours were also similar to the baseline values in all groups ($P > 0.05$).

In addition, CRP values at the postoperative 48th hour were significantly lower in Group 1 compared to Group 2 ($P < 0.05$, Table 8). CRP values at the postoperative 24th and 48th hours in all three groups were also statistically significantly higher compared to the baseline values ($P < 0.05$). Side effects are summarized in Table 9. There were no statistical differences among the groups in terms of side effects ($P > 0.05$).

Table 1. Demographic features and ASA classifications (mean ± SD).

	Group 1 (n = 5)	Group 2 (n = 15)	Group 3 (n = 15)	+P
Age (years)	36.6 ± 14.39	47.27 ± 15	45.1 ± 13.7	0.396
Sex (male/female)	9/6	8/7	9/6	0.913
Weight (kg)	69.7 ± 11.86	70 ± 17.03	79.2 ± 12.81	0.382
Height (cm)	168.4 ± 8.62	164.93 ± 9.25	170.6 ± 9.06	0.218
ASA status II/III	12/3	9/6	10/5	0.484
Duration of surgery (min)	193 ± 43.9	173.7 ± 27	191.3 ± 53.5	0.440

+P < 0.05: Statistically significant difference among the groups. ASA: American Society of Anesthesiology.

Table 2. Total epidural PCA analgesic consumption (mean ± SD).

Epidural PCA delivery (mL)	Group 1 (n = 15)	Group 2 (n = 15)	Group 3 (n = 15)	+P
Baseline	0.00	0.00	0.00	NS
1st hour	7.35	6.85	7.65	0.418
2nd hour	14.59	13.89	15.42	0.689
4th hour	26.52	27.21	28.61	0.257
6th hour	42.57	40.13	42.06	0.939
12th hour	76.04	67.56	75.36	0.614
24th hour	137.46	128.11	132.83	0.466
48th hour	248.48	238.31	237.57	0.497

+P < 0.05: Statistically significant difference among the groups. PCA: Patient-controlled analgesia.

Table 3. Comparison of VASr scores among groups (median (min–max)).

VASr	Group 1 (n = 15)	Group 2 (n = 15)	Group 3 (n = 15)	+P
Baseline	3 (2–6)	2 (2–8)	3 (2–5)	0.217
1st hour	2 (2–4)	2 (2–8)	2 (2–5)	0.656
2nd hour	2 (2–3)	2 (0–7)	2 (0–4)	0.323
4th hour	2 (1–3)	2 (0–5)	2 (0–3)	0.739
6th hour	2 (0–2)	2 (0–4)	2 (0–3)	0.939
12th hour	2 (0–2)	2 (0–4)	2 (0–2)	0.584
24th hour	1 (0–2)	2 (0–3)	0 (0–2)	0.207
48th hour	0 (0–2)	0 (0–2)	0 (0–2)	0.664

+P < 0.05: Statistically significant difference among the groups. VASr: Visual analog scale - resting.

4. Discussion

In the present study, we evaluated the effects of administration of a levobupivacaine and morphine combination via thoracic epidural catheter before and after incision and in the postoperative period on analgesic consumption, pain scores, and stress hormones. We investigated the role of timing of analgesia, which was initiated in the preoperative, intraoperative, or postoperative periods. We found that different timing of thoracic epidural analgesia had similar effects on the severity of postthoracotomy pain, analgesic consumption, and stress response among all three groups.

Table 4. Comparison of VASc scores among the groups (median (min–max)).

VASc	Group 1 (n = 15)	Group 2 (n = 15)	Group 3 (n = 15)	+P
Baseline	3 (2–7)	2 (2–8)	3 (2–5)	0.217
1st hour	2 (2–4)	2 (2–8)	2 (2–5)	0.524
2nd hour	2 (2–3)	2 (0–7)	2 (0–4)	0.219
4th hour	2 (1–3)	2 (0–6)	2 (0–3)	0.762
6th hour	2 (0–2)	2 (0–5)	2 (0–3)	0.720
12th hour	2 (0–2)	2 (0–5)	2 (1–2)	0.874
24th hour	1 (0–2)	2 (0–3)	1 (0–2)	0.267
48th hour	0 (0–2)	1 (0–2)	1 (0–2)	0.177

+P < 0.05: Statistically significant difference among the groups. VASc: Visual analog scale - coughing.

Table 5. Comparison of blood glucose levels among the groups (median (min–max)).

Blood glucose (mg)	Group 1 (n =15) *P	Group 2 (n = 15) *P	Group 3 (n = 5) *P	+P
Preoperative	99 (80–118)	112 (83–148)	101(63–134)	0.550
4th hour	130 (87–183) +0.005	152 (109–32) +*0.000	140 (87–220) *0.000	0.039+
24th hour	126 (90–164) *0.000	133 (111–166) *0.005	125 (89–240) *0.006	0.584
48th hour	126.5(86–161) *0.002	140(104–189) *0.028	146 (94–262) *0.000	0.097

+P < 0.05: Statistically significant difference among the groups.
*P < 0.05: Compared to preoperative values in the intragroup analysis.

Table 6. Comparison of insulin levels among the groups (median (min–max)).

Insulin (mg)	Group 1 (n = 15) *P	Group 2 (n = 15) *P	Group 3 (n = 15) *P	+P
Preoperative	8.6 (1.6–39.9)	8.4 (0.6–22.4)	7.9 (2–17.1)	0.771
4th hour	10.7 (2.2–52.3)	11.4 (0.7–45.9)	10.4 (2.7–27.6)	0.665
24th hour	24.9 (6.6–61.12)	11.3 (1.5–52.8)	34.5 (6.2–98.8) *0.007	0.119
48th hour	35.2 (10.7–69.2) *0.010	18.1 (1.9–90) *0.031	36.1 (7.6–120.2) *0.006	0.079

+ P < 0.05: Statistically significant difference among the groups.
*P < 0.05: Compared to preoperative values in the intragroup analysis.

Several studies have shown that acute pain behavior or extreme sensitivity of the dorsal horn neurons can be prevented by blocking afferent stimulation before the surgical incision (6,13–15). A recent metaanalysis study showed positive effects of preemptive analgesia on epidural analgesia (13), although most of the early clinical studies had negative results (11). Bong et al. (16) showed that the success of preemptive epidural analgesia is more obvious in thoracotomy procedures than in other procedures in their metaanalysis of randomized controlled trials.

Preemptive studies using combinations of epidurals, local anesthetics, and/or opioids are limited in thoracic surgery. Erturk et al. (17) compared the effects of the pre- and postoperative initiation of thoracic epidural analgesia. They used a 0.1% levobupivacaine and 2 μg/mL fentanyl combination as a bolus and epidural PCA. They reported that the epidural PCA pump delivery doses in the preemptive group were lower than in the postoperative group. The authors also found significant clinical efficacy of preemptive analgesia in the early postoperative period.

Table 7. Comparison of cortisol levels among the groups (median (min–max)).

Cortisol (mg)	Group 1 (n = 15)	Group 2 (n = 15)	Group 3 (n = 15)	+P
Preoperative	26.2 (8.6–37.5)	21.8 (7.58–45.5)	20.4 (10.7–43.8)	0.550
4th hour	24.6 (9.5–46)	27 (9.8–42.2)	29.9 (10.4–64.6)	0.201
24th hour	20.1 (5–32.4)	22.9 (2.2–30)	18.7 (2.2–34.7)	0.932
48th hour	16.6 (5.8–29.7)	19.5 (2.2–34.7)	20.9 (2–33.9)	0.651

+P < 0.05: Statistically significant difference among the groups.

Table 8. Comparison of CRP levels among the groups (median (min–max)).

CRP (mg)	Group 1 (n = 15) *P	Group 2 (n = 15) *P	Group 3 (n = 15) *P	+P
Preoperative	0.9 (0.24–4.7)	1.14 (0.1–4.6)	0.71 (0.25–2.04)	0.169
4th hour	1.17 (0.25–22.9)	1.1 (0.1–4.9)	0.78 (0.21–2.39)	0.073
24th hour	13.8 (7.29–30) *0.000	16.5 (6.8–33) *0.000	15.6 (1.4–32.6) *0.000	0.595
48th hour	14.8 (2.9–25.6) +*0.000	20.4 (7–39) +*0.000	16.1 (1.1–33.7) *0.000	0.033+

+P < 0.05: Statistically significant difference among the groups.
*P < 0.05: Compared to preoperative values in the intragroup analysis.
CRP: C-reactive protein.

Table 9. Side effects.

Side effects	**Group 1 (n = 15)**	**Group 2 (n = 15)**	**Group 3 (n = 15)**	**Total**
Shoulder pain	2	1	2	5
Nausea	4	6	7	17
Vomiting	2	2	2	6
Hypotension	2	2	1	5
Bradycardia	2	1	1	4
Itching	2	1	3	6
Constipation	0	0	0	0
Urinary retention	0	0	0	0
Respiratory depression	0	0	0	0
Excessive sedation	0	0	0	0

In another study, Özcan et al. (18) applied a combination of 1 mg/mL bupivacaine and 0.1 mg/mL morphine bolus (10 mL) via injection followed by PCA with 1 mg/mL bupivacaine and 0.05 mg/mL morphine infusion in the preoperative and the postoperative period. The authors reported that thoracic epidural analgesia applied before the surgical incision was more effective for pain management, but they did not find any difference in the analgesic consumption between the groups.

However, in our study, the local anesthetic bolus and PCA doses were higher than in the mentioned studies. Considering the absence of a significant difference in the analgesia levels among the groups, we believe that we were able to provide more effective analgesia in all groups.

Yegin et al. (19) applied 8 mL of a bolus solution of 0.25% bupivacaine and 2 mL of fentanyl (25 μg/mL) in saline via epidural catheter before anesthesia induction. The authors reported higher analgesia levels and lower

analgesic consumption in the preoperative group. Their larger sample size and usage of fentanyl with a more rapid onset may be the cause of the differing results between our study and that of Yegin and Ertürk (17,19).

In a double-blind, placebo-controlled study, Aguilar et al. (12) applied a bolus of 0.5% bupivacaine and adrenaline (1/200,000, 8 mL) through a thoracic extradural catheter before and after the surgical incision for thoracic surgery and reported no significant difference in the pain scores and requirement for additional analgesics between groups. Negative results could be explained by the insufficient afferent block for the preemptive effects.

The effectiveness of epidural analgesia before the thoracic incision was investigated in a placebo-controlled study (20). The authors applied 8 mL of 0.25% bupivacaine and 2 mL of fentanyl (50 μg/mL) via thoracic epidural catheter before the surgical incision and administered a 0.1% bupivacaine and 10 μg/mL fentanyl infusion (6 mL/h). Maximum pain scores within the first 6 h were statistically significantly lower in the patients who received preemptive analgesia. However, there were no significant differences in the pain scores after 6 h. In another study, a bupivacaine and fentanyl combination was administered in the pre- and postoperative periods in patients who underwent thoracotomy (21). Although the authors found that preoperative administration was more effective on acute pain management, analgesic requirements, and pulmonary functions, it showed little clinical significance.

Stress response can be prevented and mediator levels can be held at the preoperative levels by applying epidural anesthesia before surgical stimulation (22). Additionally, it has been suggested that epidural analgesia provided by local anesthetics or morphine should continue during the postoperative period to reduce the stress response at the maximum level (23).

Furthermore, epidural analgesia prevents surgery-induced hyperglycemic and adrenocortical responses. A local anesthetic agent applied before the surgical incision for lower abdominal surgery can provide this effect. However, epidural blockage can decrease—but cannot suppress completely—metabolic response in the upper abdominal and thoracic surgeries (24,25). This can be attributed to the persistent vagal afferents, the partial blockage of somatic afferents, and the free nerve end stimulation in the diaphragm and peritoneum (24).

The duration and extent of surgery may affect not only the pain degree but also the hormonal response to stress. Despite epidural blockage, neuroendocrine response to a major surgery can develop, and the levels can increase when the operation time is prolonged (26). In thoracic surgery there are several noxious stimuli, such as retractor placement, intercostal nerve damage, rib fractures, insertion of chest drains, and stripping of the periosteum (12). Therefore, we performed this study in patients undergoing thoracic surgery to demonstrate the effectiveness of preemptive epidural analgesia on the stress response. There is a limited number of studies evaluating hormonal responses to thoracotomy in the literature. In our study, there was no significant difference among the groups, while partial suppression was provided by epidural blockage.

In a study comparing the combination of general and epidural anesthesia with general anesthesia alone in thoracic surgery patients, it was reported that there was partial inhibition in the combined anesthesia group (27). Amr et al. demonstrated that there was no significant difference between groups with either cortisol or glucose in their study. In both groups, cortisol levels were significantly higher at 4 and 24 h in comparison with the preoperative baseline values (21). In our study, there was suppression in all postoperative measurements of cortisol levels in three groups. We found that the cortisol level at the 4th hour in Group 1 was lower than the preoperative value, although this was not statistically significant. This may be due to the small positive effects of preemptive epidural blockage.

In this study the blood glucose, insulin, and CRP levels tended to increase compared to the preoperative values for 48 h. The suppression of CRP and insulin levels at the 4th hour, which is the early phase, was detected in all groups. Based on these findings, we believe that we provided effective epidural analgesia and similar suppression in the three groups. We also found that blood glucose levels at the postoperative 4th hour were statistically significantly higher in Group 2 than in Group 1. This discrepancy can be explained by the higher preoperative values in Group 2.

Insulin, an anabolic and hypoglycemic hormone, decreases after trauma, unlike glucose and cortisol. This helps continuation of hyperglycemia and protection of the metabolic situation in vital organs (28). In our study, increased insulin levels after surgery compared to baseline levels may be due to the suppression of the stress response and elevated glucose levels.

We think that a limitation of the present study may be the smaller number of patients recruited in comparison with other trials.

In conclusion, the application of thoracic epidural analgesia before and after surgical incision and in the postoperative period did not result in a significant difference in the severity of postthoracotomy pain and stress response in all groups. Based on our results, we suggest that epidural levobupivacaine combined with morphine provides effective and safe analgesia and can partially suppress the surgical stress response. However, further large-scale, long-term studies are required to establish a definite conclusion.

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