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The effect of preemptive thoracic epidural analgesia on long-term wound pain following major thoracotomy

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Aim: To evaluate the effects of the performance of preemptive epidural analgesia in major thoracotomies on chronic postthoracotomy pain.

Materials and methods: A total of 60 patients with ASA I–II status between the ages of 18 and 75 years who planned to have elective thoracotomy were randomized into 3 groups. In all cases, an epidural catheter was placed at the 6th–7th or 7th–8th thoracic intervals, preoperatively. Patients in the control group (n = 20) did not receive epidural analgesics before and during the operation, and preoperative analgesia was provided by remifentanil infusion. In the incision-sensitized group (n = 20), patients had remifentanil infusion preoperatively and 0.1% levobupivacaine (10–15 mL) was given through the epidural catheter 10 min after the surgical incision. Considering that epidural analgesia reached an adequate level 20 min after the injection, the remifentanil infusion was stopped. In the preemptive analgesia group, patients (n = 20) received 10–15 mL of 0.1% levobupivacaine at the 2nd dermatome superior and inferior to the incision dermatome through the epidural catheter for analgesia before anesthesia induction. The pain levels of the patients were evaluated at postoperative months 1, 3, and 6 using a visual analog pain scale.

Results: When the pain of the patients in the chronic period were compared, no statistically significant difference was found among all 3 groups ($P > 0.05$).

Conclusion: We suggest that thoracic preemptive epidural analgesia application before the incision is not superior to intraoperative or postoperative thoracic epidural analgesia in prevention or attenuation of chronic postthoracotomy pain after major thoracotomy operations.

Key words: Preemptive epidural analgesia, thoracotomy, chronic pain

1. Introduction

The type of pain observed after thoracotomy is an acute traumatic pain. Continuation of pain longer than 2 weeks is defined as postthoracotomy pain syndrome. Thoracotomy as well as extremity amputation are thought to be surgical approaches with a high risk rate for chronic pain development (1). In approximately 50% of cases, the pain is expected to be relieved in 1 week with effective analgesia in the early period of operation. In various publications, it was reported that chronic postthoracotomy pain can last between 2 months and 5 years (2–6).

Nociception blockage by analgesic application before a painful stimulus is defined as preemptive analgesia. If analgesic treatment is started before the painful stimulus, difficulties in treating postoperative pain in such cases may be observed, because peripheral sensitivity and central nervous system hyperexcitability could have developed (7,8).

In this study, we aimed to investigate the effects of preemptive thoracic epidural analgesia in chronic postthoracotomy pain, which is observed after major thoracotomy operations.

2. Materials and methods

This study was approved by the institutional review board and written informed consent was received from patients. A total of 60 patients with ASA I–II status at preanesthetic examination, who had no concomitant disease and who planned to have elective thoracotomy between April 2009 and June 2010 in the Department of

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Chest Surgery, were enrolled in this study. They received education about the visual analog scale (VAS) scoring and the "Patient Satisfaction Scale" so that could grade their pain and satisfaction levels during the postoperative period. Sex, age, weight, and contact phone numbers of patients were noted preoperatively. All patients fasted for 8 h preoperatively.

Epidural catheters were placed preoperatively into all patients at the 6th–7th or 7th–8th thoracic intervals under sterile conditions. After the epidural catheter was placed in all patients, a 3-mL test dose of 2% lidocaine (Aritmal Vial 2%, 5 mL, Osel, İstanbul) containing 1/200,000 adrenalin (Adrenalin Vial 0.25 mg, Galen, İstanbul) was injected.

In this double-blind, randomized, prospectively planned study, participants, who were not previously informed about to which study group they would be assigned, were divided into 3 groups each comprising 20 participants and randomized using the envelope method. Control group (Group C, n = 20) patients did not receive epidural analgesic medication before and during the operation through epidural catheters, and preoperative analgesia was provided by 0.25–0.50 μg kg^{-1} h^{-1} remifentanil (Ultiva Vial, 2 mg, GlaxoSmithKline, Verona, Italy) infusion. For the incision-sensitized group (Group S, n = 20), preoperative analgesia was started with remifentanil infusion of 0.25–0.50 μg kg^{-1} h^{-1} and, 10 min after surgical incision, 10–15 mL of 0.1% levobupivacaine (Chirocaine Vial 0.5%, 10 mL, Abbott, Fornebu, Norway) was administered through the catheter. When the epidural analgesia was considered to have reached an adequate level, remifentanil infusion was discontinued 20 min after the epidural injection. Increases of more than 20% in arterial tension and pulse rate were accepted as inadequate epidural analgesia, and these cases were excluded. In the preemptive analgesia group (Group P, n = 20), participants received 10–15 mL of 0.1% levobupivacaine at the 2nd dermatome superior and inferior to the incision dermatome (between T4 and T10) through the epidural catheter for analgesia before anesthesia induction, and the adequacy of the analgesia was evaluated by hot-cold test application. Perioperative analgesia was provided by 10 mL of 0.1% levobupivacaine injection every 45 min.

All patients received 100% oxygen at the rate of 10 L/min for 3 min. Patients were intubated with a double lumen endobronchial tube after adequate muscle relaxation was provided with 0.8 mg/kg rocuronium bromide (Esmeron Vial, 50 mg/5 mL, Organon, Oss, the Netherlands) after 2 mg/kg propofol (Propofol Vial 2%; 50 mL, Fresenius Kabi, Leipzig, Germany) induction. The placement of the endobronchial tube was confirmed by fiberoptic bronchoscopy.

Maintenance of anesthesia was provided by sevoflurane (Sevorane Liquid, 250 mL, Abbott, Berkshire, UK) in 40% oxygen with minimum alveolar concentration values ranging from 1 to 1.5. The oxygen amount was increased according to the saturation of the patient during single lung ventilation. During the operation, for perioperative analgesia, participants in Group C received a remifentanil infusion of 0.25–0.50 μg kg^{-1} h^{-1}; participants in Group S received a remifentanil infusion of 0.25–0.50 μg kg^{-1} h^{-1} for 30 min after the surgical incision, and then 10 mL of 0.1% levobupivacaine injection every 45 min through the epidural catheter (cases of increases of more than 20% in arterial tension and pulse rate were accepted as inadequate epidural analgesia and were excluded); and participants in Group P received 10 mL of 0.1% levobupivacaine injection every 45 min through an epidural catheter.

After surgery was completed, 1.5 mg of neostigmine (Neostigmin Vial, 0.5 mg/mL, Adeka, Samsun, Turkey) and 0.5 mg of atropine (Atropin Sulfat Vial, 0.5 mg/mL, Galen) were applied for antagonism of muscle relaxant. After extubation, the patients were followed in the postoperative monitorization room for 30 min, and then they were transferred to the intensive care unit of the surgery department.

In all 3 groups, postoperative analgesia was provided by 3 mg of morphine (Morfin HCl Vial, 10 mg, Galen) + 50 μg of fentanyl (Fentanyl Citrate Vial, Antigen Pharmaceuticals, Dublin, Ireland) in 15 mL of isotonic solution given through the epidural catheter just after the operation while skin sutures were being placed. For all patients, analgesia was followed for 48 h and a postoperative epidural analgesic solution was given in 12-h intervals. Having received education about the VAS, patients informed their clinical assistant when their VAS score was ≥3, and an additional dose of postoperative epidural analgesic solution was then injected.

For all patients, the VAS score, blood pressure, and heart beat rate were recorded at postoperative hours 1, 4, 24, and 48. The VAS scores of patients that attended the follow-up visits at postoperative months 1, 3, and 6, were recorded in face-to-face interviews, whereas patients that could not attend the visits were contacted by phone and the information was obtained without informing the participants that they were also being recorded. It was expected that patients for whom the VAS score was ≥3 at postoperative months 1, 3, and 6 would have chronic postthoracotomy pain. Likewise, patients were asked about their patient satisfaction levels and their responses were recorded during discharge and at the 6th postoperative month.

The results were statistically analyzed. Statistical analyses were performed with SPSS 15.0. The Kruskal–Wallis test was employed to compare age, weight, duration of anesthesia and surgery, blood pressure, pulse rate, saturation detected at the fingertips, and VAS and patient

satisfaction levels among the groups, whereas the Mann–Whitney test was employed for statistical evaluation between binary groups.

In this present study, the primary objective was to decrease chronic postthoracotomy pain after major thoracotomy operations through preemptive thoracic epidural analgesia. The number of cases required to meet this primary objective was detected by power analysis. In their prospective study involving 84 cases, Perttunen et al. (9) reported that the incidence of postthoracotomy chronic pain at month 3 and month 6 and at year 1 was 80%, 75%, and 61%, respectively. We decided that we could decrease 30% of chronic postthoracotomy pain after major thoracotomy operations by applying preemptive thoracic epidural analgesia. Power analysis revealed that, in order to decrease the chronic postthoracotomy pain from 75% to 45% at month 6 (type-1 error, $\alpha = 0.05$; type-2 error, $1 - \beta = 0.8$), each group needed comprise 20 participants. Acute pain levels of patients in the first 48 h as well as patient satisfaction levels at discharge and at month 6 were defined as secondary objectives. The statistical level of significance was accepted as $P < 0.05$.

3. Results

A total of 3 participants who died in the 6-month follow-up and 2 participants with wound infection at the incisions were excluded from the study, and new participants that were compliant with the inclusion criteria were enrolled.

The demographic characteristics of the cases are shown in Table 1. No statistically significant difference was found among groups in terms of age, weight, and sex ($P > 0.05$). The durations of anesthesia and surgery were similar in all 3 groups (Table 2). No bradycardia, hypotension, or hypoxia occurred in any of the cases during the postoperative phase.

3.1. Postoperative VAS score values

VAS scores among groups at postoperative hours 1, 4, 24, and 48; at discharge; and at postoperative months 1, 3, and 6 are given in Table 3.

No statistically significant difference was found between groups in terms of VAS scores at postoperative months 1, 3, and 6 ($P > 0.05$). The VAS scores at postoperative month 1 were ≥3 at 20% for Group C, 15% for Group S, and 10% for Group P. At the 3rd month, the VAS score values were detected as ≥3 for Groups C, S, and P at 20%, 20%, and 15%, respectively. The results for the 6th month were 30%, 25%, and 20%, respectively. No statistically significant difference was found between numbers in respect to the presence of postthoracotomy pain at months 1, 3, and 6 ($P > 0.05$; Table 4). Moreover, the VAS scores for Group P at postoperative hours 1, 4, 24, and 48 were not statistically more significant than those values in Groups C and S ($P > 0.05$).

3.2. Postoperative patient satisfaction values

Patient satisfaction scores at discharge and at postoperative month 6 are given in Table 5. When all 3 groups were compared in respect to patient satisfaction scores, no statistically significant difference was found between the time of discharge and postoperative month 6 ($P > 0.05$).

4. Discussion

Postthoracotomy chronic pain is a severe problem that affects the majority of patients and decreases the quality of life. Although our knowledge about algology and drug applications with new devices have both improved, insufficient treatment of pain in the postoperative phase still presents an important issue.

Landreneau et al. (10) reported cases of postthoracotomy pain syndrome after trauma, such as intercostal neurinoma, rib fractures, local infection or pleurisy, costochondritis or costochondral dislocation, and local tumor recurrence. Intercostal nerve damage is the leading factor among the etiological factors in the development of chronic pain after thoracotomy.

Steegers et al. (11) reported on a total of 204 patients, of which 144 had thoracotomy and 60 had video-assisted thoracoscopic surgery (VATS). They found that the incidence of chronic pain 6 to 42 months after thoracotomy was 40% for thoracotomy and 47% for VATS. Likewise, Maguire et al. (12) conducted a study of 948 cases of thoracotomy and postoperative chronic pain was observed in 57% of cases within 7–12 months of the surgery, in 36% of cases within 4–5 years of the surgery, and in 21% of cases within 6–7 years of surgery. In our study, we defined the incidence of chronic pain in the 1st month after thoracotomy as 20% for Group C, 15% for Group S, 10% for Group P, and 20% overall. In the postoperative 3rd month, we detected the incidence of pain as being 20% for Group C, 20% for Group S, 15% for Group P, and 18.3%

Table 1. Demographic characteristics of cases. All values are given as mean ± standard deviation, $P > 0.05$.

	Group C (n = 20)	Group S (n = 20)	Group P (n = 20)	P-value
Age (years)	52.20 ± 17.05	45.00 ± 17.46	50.90 ± 16.12	0.409
Weight (kg)	71.25 ± 15.23	67.45 ± 13.20	73.70 ± 14.91	0.453
Sex (M/F)	15/5	15/5	15/5	1.000

Group C: control group; Group S: incision-sensitized group; Group P: preemptive analgesia group.

Table 2. Durations of anesthesia and surgery in cases. All values are given as mean ± standard deviation, P > 0.05.

Time	Group C (n = 20)	Group S (n = 20)	Group P (n = 20)	P-value
Duration of anesthesia (min)	167.75 ± 52.97	198.75 ± 52.16	198.75 ± 53.45	0.096
Duration of surgery (min)	138.50 ± 53.21	168.00 ± 51.87	169.25 ± 52.67	0.106

Group C: control group; Group S: incision-sensitized group; Group P: preemptive analgesia group.

Table 3. Postoperative VAS score values. All values are given as mean ± standard deviation, P > 0.05.

Time	Group C (n = 20)	Group S (n = 20)	Group P (n = 20)	P-value
Hour 1	1.15 ± 0.36	1.10 ± 0.30	1.10 ± 0.44	0.895
Hour 4	1.15 ± 0.36	1.05 ± 0.22	1.10 ± 0.44	0.662
Hour 24	1.15 ± 0.36	1.05 ± 0.22	1.10 ± 0.30	0.579
Hour 48	1.20 ± 0.41	1.20 ± 0.41	1.30 ± 0.47	0.693
Discharge	1.50 ± 0.51	1.35 ± 0.48	1.35 ± 0.48	0.541
Month 1	2.00 ± 0.91	1.65 ± 0.74	1.75 ± 0.78	0.436
Month 3	1.90 ± 0.96	1.80 ± 1.00	1.65 ± 0.87	0.664
Month 6	2.10 ± 0.96	1.95 ± 0.99	1.70 ± 0.92	0.348

Group C: control group; Group S: incision-sensitized group; Group P: preemptive analgesia group.

overall. For the postoperative 6th month, the results were 30% for Group C, 25% for Group S, 20% for Group P, and 25% overall.

Blockage of nociception with analgesic application before painful stimulus is known as preemptive analgesia. Decreasing acute pain after tissue damage, preventing pathological modulations of the central nervous system related to pain, and preventing continuation of postoperative pain and chronic pain development are among the objectives of preemptive analgesia (13). If analgesic treatment is initiated after the painful stimulus, difficulties in postoperative pain treatment can be encountered because peripheral hypersensitivity and central nervous system hyperexcitability may develop in such cases (14,15). The idea of controlling postoperative pain starting from the preoperative phase, the concept of preemptive analgesia, was first discussed in 1933 by Crile (16). Postoperative pain develops by evaluation of the nociceptive afferent stimuli that have initiated at the incision region at surgical interventions, at the medulla spinalis, and in the central nervous system (17). The aim of preemptive analgesia is to cause central sensitization by blocking nociceptive afferent pain pathways in the peripheral and central nervous systems, preventing postoperative pain development (18,19).

In their metaanalysis in which 6 studies and 458 cases were evaluated, Bong et al. (20) reported that preemptive thoracic epidural analgesia significantly decreased the pain with respect to the controls at postoperative hours 28 and 48, but effective or significant differences were not found with regard to chronic pain at the 6th month. In this study, we found that preemptive epidural analgesia showed no superiority in decreasing pain in thoracotomy cases during any of the postoperative acute or chronic phases.

Ryu et al. (7) investigated whether ketamine use in preemptive analgesia had any effects on pain after thoracotomy. They evaluated 133 cases of thoracotomy prospectively. The patients were divided into 2 groups: the 1st group received 0.12% levobupivacaine + 2 μg/mL fentanyl + 0.2 mg/mL ketamine through a thoracic epidural catheter, and the 2nd group received 0.12% levobupivacaine + 2 μg/mL fentanyl. Ryu et al. used VAS scoring 2 weeks and 3 months postoperatively for pain query and reported that low-dose epidural ketamine, administered for preemptive analgesic reasons, had no effect on preventing chronic postthoracotomy pain.

In our study, we provided postoperative analgesia to all 3 groups with thoracic epidural analgesia. We detected that preemptive thoracic epidural analgesia showed no superiority for the control group receiving postoperative

Table 4. Distribution of cases with VAS score of ≥3. Data are given as number and percentage.

Time	VAS	Group C		Group S		Group P		P
		N	%	N	%	N	%	
Postop. Hour 1	≥3	1	5	1	5	1	5	1.000
	<3	19	95	19	95	19	95	
Postop. Hour 4	≥3	0	0	0	0	0	0	1.000
	<3	20	100	20	100	20	100	
Postop. Hour 24	≥3	0	0	0	0	0	0	1.000
	<3	20	100	20	100	20	100	
Postop. Hour 48	≥3	0	0	0	0	0	0	1.000
	<3	20	100	20	100	20	100	
Discharge	≥3	0	0	0	0	0	0	1.000
	<3	20	100	100	100	100	100	
Month 1	≥3	4	20	3	15	2	10	0.680
	<3	16	80	17	85	18	90	
Month 3	≥3	4	20	4	20	3	15	0.896
	<3	16	80	16	80	17	85	
Month 6	≥3	6	30	5	25	4	20	0.769
	<3	14	70	15	75	16	80	

Group C: control group; Group S: incision-sensitized group; Group P: preemptive analgesia group.

Table 5. Postoperative patient satisfaction score values. All values are given as mean ± standard deviation, P > 0.05.

Time	Group C	Group S	Group P	P
At discharge	3.65 ± 0.48	3.90 ± 0.30	3.85 ± 0.36	0.116
Month 6	3.00 ± 0.91	3.10 ± 0.91	3.40 ± 0.82	0.314

Group C: control group; Group S: incision-sensitized group; Group P: preemptive analgesia group.

epidural analgesia in the postoperative early phase; furthermore, it did not show superiority for long-term pain attenuation.

In conclusion, we investigated the effects of thoracic epidural analgesia, which is induced preemptively for chronic postthoracotomy pain after major thoracic operations. In all cases, we observed that with thoracic epidural analgesia after major thoracic operations, preemptively or intraoperatively or postoperatively, all methods had efficient analgesia without showing any superiority to each other. However, according to the results of pain follow-up at postoperative month 6, preemptive application of thoracic epidural analgesia before the incision was made did not show any superiority to intraoperatively initiated or postoperatively initiated thoracic epidural analgesia; therefore, we think that multimodal pain treatment methods are required for prevention of chronic postthoracotomy pain.

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