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Original Article

The effect of pre-emptive intravenous Dexketoprofen + thoracal epidural analgesia on the chronic post-thoracotomy pain

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Abstract: Post thoracotomy chronic pain is a severe problem that affects the majority of patients and decreases the quality of life. The purpose of this study is to evaluate the long-term effects of thoracal epidural levobupivacaine and intravenous dexketoprofen analgesia formed pre-emptively on the wound site pain after major thoracotomy operations. This randomised, prospective and double-blind study was performed with 60 patients undergoing thoracic surgery. Patients were divided into three groups; Control Group (Group C), Pre-emptive Epidural Group (Group PE) and Pre-emptive Dexketoprofen + Epidural Group (Group PED). Patients in the Group C did not receive epidural analgesics and i.v. dexketoprofen before and during the operation. 10-15 ml 0.125% levobupivacaine was given to cases in Group PE pre-emptively through epidural catheter before the anesthesia induction. The cases in Group PED were given 10-15 ml 0.125% epidural levobupivacaine and 50 mg dexketoprofen with i.v. infusion pre-emptively. The VAS score was found to be lower in Group PED during postoperative 24 and 48 hours and before the discharge ($P<0.05$). The VAS score was similar in all groups during the first and third months ($P>0.05$). A statistically significant decrease was determined in the VAS score in Group PED during the sixth month, compared to the other groups ($P<0.05$). When the scores of Patient Satisfaction Scale (PSS) of the cases were compared, they were found to be higher in Group PED as statistically significant during the discharge period ($P<0.001$). Scores of PSS were higher in Group PED as statistically significant during the postoperative month 6 ($P = 0.008$). Combined application of pre-emptive intravenous dexketoprofen and thoracal epidural analgesia reduce the chronic post-thoracotomy pain.

Keywords: Pre-emptive epidural analgesia, post-thoracotomy pain, dexketoprofen

Introduction

Several pain management methods are applied in patients who have undergone a thoracotomy operation. NSAID's, parenteral opioids, intercostal nerve block, intercostal cryoneurolysis, intrapleural local anaesthetic application, local anaesthetic and/or opioid combination through an epidural catheter are among these methods. Postoperative epidural analgesia seems to be superior among all [1, 2].

Pre-emptive analgesia was formulated by Crile [3]. This is an antinociceptive treatment which prevents the establishment of altered processing of afferent input that amplifies the postoperative pain [4].

The primary objective of this study is to evaluate the long-term effects of thoracal epidural local anaesthetic levobupivacaine formed pre-emptively, and intravenous dexketoprofen analgesia, which is NSAID on wound site pain after major thoracotomy operations. Conversely, the secondary objective is to evaluate the acute pain levels of the cases within the first 48 hours, as well as their satisfaction levels during the discharge period and month 6.

Materials and methods

This study was determined as randomised, double-blind and prospective with the permission of Ethics Committee of Atatürk University Medical Faculty and the decision of the Surgical Board. 60 18-75 year old cases, for whom thoracotomy was planned by the Thoracic Surgery clinic under elective conditions between April 2010-August 2011 and who had no concomitant systemic disease with functional limitation and were evaluated as ASA I, II in their pre-anaesthetic examinations, were included in the study after receiving their written informed consents.

Pre-anaesthetic examinations of all cases were performed one day before the operation. Cases with appropriate criteria for our study were informed about the study and their written informed consents were received. Cases were trained about the VAS (Visual analogue scale) score and patient satisfaction scale, and were informed broadly how to evaluate their pain levels and patient satisfaction rates in the postoperative period.

An epidural catheter was inserted to all cases using an 18 Gauge Touhy needle (Egemen epidural set, Izmir, Turkey) with the help of the negative pressure hanging drop method from the levels of Thoracic 6-7 or Thoracic 7-8 in the preoperative period. Following the determination of epidural catheter, 2 ml 2% lidocaine (Jetmonal® 2%, 5 ml amp. Adeka, Istanbul, Turkey) was applied to cases as a test dose. The cases, who were not informed about which study group they were included in, were divided into 3 groups involving 20 individuals with the random envelope method.

The Control Group (Group C, n = 20); no i.v. dexketoprofen (Arveles® 50 mg/2 ml amp. Menarini Group, Florence, Italy) and pre-emptive epidural analgesic medication was applied to cases. Intraoperative analgesia was provided with 50-100 mcg/h Fentanyl citrate (Fentanyl Citrate Ampoule®, Antigen Pharmaceuticals, Munchen, Germany) and O_2/N_2O 40-60%.

The Pre-emptive Epidural Group (Group PE, n = 20): 10-15 ml 0.125% levobupivacaine (Chirocain® 5 mg/ml, 10 ml bottle, Abott, Norway) was given to cases in 5 ml with intervals of 5 minutes pre-emptively through epidural catheter before the anaesthesia induction to provide the analgesia at two dermatome levels below and above the surgical incision dermatome (T4-T10). Sufficiency of the analgesia was determined by performing hot-cold test and the anaesthesia induction was then started. Intraoperative analgesia was provided with 10 ml 0.125% Levobupivacaine injection, which was repeated every 60 minutes through epidural catheter.

The Pre-emptive Dexketoprofen + Epidural Group (Group PED, n = 20): 10-15 ml 0.125% levobupivacaine (Chirocain® 5 mg/ml, 10 ml bottle, Abbott, Norway) was given to cases in 5 ml with intervals of 5 minutes pre-emptively through an epidural catheter before the anaesthesia induction to provide the analgesia at two dermatome levels below and above the surgical incision dermatome (T4-T10). Sufficiency of the analgesia was determined by performing a hot-cold test. In addition, 50 mg dexketoprofen trometamol (Arveles® 50 mg/2 ml amp. Menarini Group, Florence, Italy) was given within 100 ml 0.9% NaCl with i.v. infusion in 15 minutes, and it was finished 15 minutes before the surgical incision. Intraoperative analgesia was provided with 10 ml 0, 125% Levobupivacaine injection, which was repeated every 60 minutes through epidural catheter.

Pre-oxygenation was provided for all cases with 6-8 L/minute 100% O_2 (3-5 minutes). Following 2 mg/kg propofol induction (Propofol® Flakon 2% 50 ml®, Fresenius Kabi, Munchen, Germany) and the sufficient muscle relaxation that was provided with 0.6-1 mg/kg rocuronium bromide (Esmeron® Flakon 50 mg/5 ml®, Organon, Netherlands), the cases were intubated using a double-lumen endobronchial tube. The area of the endobronchial tube was confirmed with fiberoptic bronchoscopy. The maintenance of the anaesthesia was provided with 6-8% Desflurane (Suprane® Liquid 240 ml®, Baxter, Istanbul, Turkey) within 45% O_2, between MAC (minimum alveolar concentration) 1-1.5. During one-lung ventilation (OLV), the amount of oxygen was increased according to the saturation of the case.

Cases in Group C were given 50 mcg/h Fentanyl and O_2 + 50-60% N_2O for the analgesia in the intraoperative period. Dosage of the Fentanyl was increased to 100 mcg/h during the one

Table 1. Demographic characteristics of the cases*

	Group C (n = 20)	Group PE (n = 20)	Group PED (n = 20)	*P* Value[a]
Age (year)	45.95±18.248	51.05±19.324	44.35±19.712	0.515
Weight (kg)	63.90±7.867	72.20±15.787	68.55±11596	0.106
Gender (M/F)	10/10	15/5	11/9	0.233

Group C, Control Group; Group PE, Pre-emptive Epidural Group; Group PED, Pre-emptive Epidural + Dexketoprofen Group. *P>0.05 between the cases. [a]One way ANOVA.

lung ventilation. In Group PE, 10 ml 0.125% Levobupivacaine injection was applied for intraoperative analgesia, which was repeated every 60 minutes through epidural catheter. Cases with an increase in the arterial tension and pulse over 20% were evaluated as insufficient epidural analgesia and excluded from the study. In Group PED, on the other hand, 10 ml 0.125% Levobupivacaine injection, which was repeated every 60 minutes, was applied through an epidural catheter. At the end of the operation, 1.5 mg neostigmine (Neostigmin® Ampoule 0.5 mg/ml, Adeka, Samsun, Turkey) and 0.5 mg atropine (Atropine Sulphate® Ampoule 0.5 mg/ml, Galen, Istanbul, Turkey) were applied for the antagonism of the muscle relaxant.

Postoperative analgesia of the cases in all three groups was provided with 3 mg morphine (Morphine HCl® Ampoule 10 mg, Galen, Istanbul, Turkey) + 50 mcg fentanyl (Fentanyl Citrate® Ampoule, Antigen Pharmaceuticals, Munchen, Germany) within 15 ml 0.9% NaCl through epidural catheter shortly before the operation while stitching the skin sutures. Analgesia of the cases was followed for 48 hours and postoperative epidural analgesic fluid was applied at the intervals of 12 hours. When the VAS score became ≥3, an additional dose of postoperative epidural analgesic fluid was applied. In addition, a postoperative 50 mg dexketoprofen trometamol was given to Group PED with i.v. infusion in 15 minutes within 100 ml 0.9% NaCl, 12 hours after the first dexketoprofen dose.

The VAS scores, arterial blood pressures and heart rates of all cases were recorded by Assistant of Department of Anaesthesiology and Reanimation, who had completed at least two years in the department, in 1st, 4th, 24th and 48th postoperative hours without knowing the groups of the cases. Similarly, the VAS score was questioned and recorded by making face-to-face interviews with the cases who could come for the examination, and calling those who could not, during the 1st, 3rd, and 6th postoperative months, without knowing the groups of the cases. The existence of chronic post-thoracotomy pain was accepted in cases with a VAS score of ≥3 during the 1st, 3rd, and 6th postoperative months. Patient satisfaction was also questioned and recorded following the discharge of the cases and during postoperative month 6.

The pain of cases was evaluated with a 10 cm non-graded horizontal line VAS, ends of which are marked as “no pain” on the left and “the worst conceivable pain” on the right, and involved no rating. In the evaluation of the VAS score, 0 was accepted as no pain, 10 was accepted as the worst conceivable pain; and the pain level was evaluated on the scale between 0-10. Patient satisfaction was evaluated using the 4-point scale. 1 = very dissatisfied, 2 = somewhat satisfied, 3 = rather satisfied and 4 = completely satisfied.

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. [5] reported that the incidence of post thoracotomy chronic pain during month 3 and month 6, and year 1 was 80%, 75%, and 61%, respectively. We decided that we could decrease 30% of the chronic post thoracotomy pain after major thoracotomy operations by applying pre-emptive thoracic epidural analgesia by adding pre-emptive intravenous dexketoprofen. Power analysis revealed that, in order to decrease the chronic post thoracotomy pain from 75% to 45% during month 6 (type-1 error, $\alpha = 0.05$; type-2 error, $1-\beta = 0.8$), each group needed to comprise of 20 participants. Acute pain levels of the patients in the first 48 h as well as patient satisfaction levels at discharge and during month 6 were defined as secondary objectives. The statistical level of significance was accepted as $P<0.05$.

The results were statistically analysed. SPSS 20.0 (Statistical Package for Social Sciences) software package was used to conduct the statistical analyses. One way ANOVA test was used

Table 2. Durations of anaesthesia and surgery of the cases*

Duration	Group C (n = 20)	Group PE (n = 20)	Group PED (n = 20)	*P* Value[a]
Anaesthesia Duration (min.)	161.75±58.720	148.50±45.771	178.00±51.026	0.209
Surgery Duration (min.)	142.25±56.510	122.75±47.834	155.25±51.388	0.148

Group C, Control Group; Group PE, Pre-emptive Epidural Group; Group PED, Pre-emptive Epidural + Dexketoprofen Group. *P>0.05 between the cases. [a]One way ANOVA.

Table 3. Postoperative VAS score values*

Period	Group C (n = 20)	Group PE (n = 20)	Group PED (n = 20)	*P* Value[a]
Postop	0.45±0.826	1.10±0.968	0.80±0.894	0.081
Hour 1	1.40±0.883	1.25±0.910	1.40±1.314	0.874
Hour 4	1.20±1.105	1.10±1.021	1.00±1.298	0.859
Hour 24	1.15±0.875	1.40±0.940	0.40±0.681	0.001**
Hour 48	1.00±0.858	1.30±1.031	0.40±0.754	0.008**
Discharge	1.60±0.883	1.90±0.308	0.20±0.616	0.000***
Month 1	1.90±0.852	1.90±0.968	1.70±1.490	0.814
Month 3	2.00±1.026	1.40±1.142	1.20±1.322	0.088
Month 6	1.85±1.496	1.15±1.348	0.60±1.142	0.017**

Group C, Control Group; Group PE, Pre-emptive Epidural Group; Group PED, Pre-emptive Epidural + Dexketoprofen Group. *All values are given as mean ± Standard Deviation. **P<0.05. ***P<0.001. [a]One way ANOVA.

for the between-group comparison of demographic findings, such as age, weight, duration of anaesthesia, duration of surgery, arterial tension (AT), pulse (PI), and oxygen saturation (SpO_2) and VAS scores. Kruskal-wallis test was used for the PSS scores. P<0.05 was accepted to be statistically significant.

Results

Demographic characteristics of the cases and their durations of anaesthesia and surgery are illustrated in **Tables 1**, **2**.

Postoperative VAS score

1. Mean VAS score was similar in all groups during the early postoperative period (in the hours 0, 1, and 4) (P>0.05), (**Table 3**).

2. Mean VAS score was found to be lower in a statistically significant way in Group PED compared to Group C and Group PE, in the measurements made during the postoperative hours 24 and 48 and discharge (P<0.05), (**Table 3**).

3. Mean VAS scores were similar in all groups during the first and third months (P>0.05), (**Table 3**).

4. Mean VAS score was found to be lower in Group PED compared to other groups in a statistically significant way in the sixth month (P<0.017, **Table 3**).

5. VAS ≥3 was found at a rate of 25% in Group C, 15% in Group PE and 20% in Group PED in the first month. It was found at a rate of 20% in Group C, 20% in Group PE and 20% in Group PED in the third month. And finally, VAS ≥3 was found at a rate of 30% in Group C, 20% in Group PE, and 10% in Group PED in the sixth month.

Patient Satisfaction Score(PSS)

1. PSS scores were found to be higher in a statistically significant way in Group PED at the discharge measurement point, compared to other groups (P<0.001, **Table 4**).

2. PSS scores were found to be higher in a statistically significant way in Group PED at the sixth-month measurement point, compared to other groups (P = 0.008, **Table 4**).

Discussion

Chronic post-thoracotomy pain is a serious problem, which affects a significant number of cases and decreases their life quality. The pain is expected to alleviate in approximately 50% of the cases with the help of an efficient analgesia within one week during the early postoperative period. A pain that lasts for more than two weeks is assessed as "Chronic Post-thoracotomy Pain Syndrome". It is stated that chronic post-thoracotomy pain might last for a period between two months and five years [6, 7].

In their study on 948 cases who had undergone thoracotomy, Maguire et al. [8] determined the postoperative chronic pain as 57% between 7-12 months, 36% between 4-5 years and 21% between 6-7 years. In their study on 85 cases who had undergone thoracotomy, Gotoda et al. [9] determined chronic post-thoracotomy pain

Table 4. Distribution of patient satisfaction scores between groups*

Period	PSS	Group C (n = 20)		Group PE (n = 20)		Group PED (n = 20)		*P* Value[a]
		Number	%	Number	%	Number	%	
Discharge	3	15	75	17	85	0	0	<0.001**
	4	5	25	3	15	20	100	
Month 6	3	11	55	9	45	2	10	= 0.008***
	4	9	45	11	55	18	90	

Group C, Control Group; Group PE, Pre-emptive Epidural Group; Group PED, Pre-emptive Epidural + Dexketoprofen Group. *Data are given as number and %; **PSS score was found to be higher in a statistically significant way in Group PED at the discharge measurement point, compared to the other groups P<0.001; ***PSS score was found to be higher in a statistically significant way in Group PED at the sixth-month measurement point, compared to the other groups P<0.05. [a]Kruskal-wallis test.

experienced by 50 cases in the postoperative day 1, 60 cases 1 month after the surgery, and 35 cases 1 year after the surgery. In a prospective study that involved 67 cases, Perttunen et al. [5] determined the incidence of chronic post-thoracotomy pain respectively as 80% in the 3rd month, 75% in the sixth month and 61% in the first year. They also stated that the incidence of severe pain was 3-5%. This study revealed that the incidence of chronic post-thoracotomy pain was respectively 25%, 20%, 30% for Group C in the postoperative months 1, 3 and 6; 15%, 20%, 20% for Group PE; and 20%, 20%, 10% for Group PED.

Pre-emptive analgesia should prevent not only the peripheral sensitisation and central sensitisation, but also the inflammatory and neuropathic pain types [10]. People who argue that pre-emptive analgesia is an effective method in clinics also argue that the approach to postoperative analgesia should involve both incisional and inflammatory damage [11].

The aim of the pre-emptive analgesia is to decrease the primary and secondary hyperalgesia, allodynia and changes of the receptive area on dorsal horn cells by preventing the peripheral and central sensitisation, which is formed against a painful stimulant [1]. The purpose of treatment of non-steroid anti-inflammatory drugs is to decrease or prevent the release of several neurotransmitter and inflammatory mediators, which increase the sensitivity of peripheral nociceptors. Cyclooxygenase inhibitors show their effect by decreasing prostaglandin synthesis and blocking the response of endogenous mediators of inflammation in the tissue, which is exposed to the greatest damage or trauma [12] .

In their meta-analysis study that involved 6 studies with 458 cases, Bong et al. [13] stated that regarding the cases that had pre-emptive epidural analgesia and developed major thoracotomy, the pain significantly decreased in the group that had pre-emptive thoracal epidural analgesia in the 24 and 48 postoperative hours, compared to the control group; however, no efficient and significant difference was observed in the 6th month. Based on this consequence, they determined that while pre-emptive analgesia is effective on acute pain, it causes no significant change on chronic pain. In their study that involved 60 cases, Can et al. [1] determined that pre-emptive epidural analgesia have no superiority over the intraoperative and postoperative epidural group in decreasing the pain during both the postoperative acute period and the chronic period in cases that underwent thoracotomy. In this study, which was conducted with the multimodal approach, VAS scores were similar between the groups during the early postoperative period (in the hours 0, 1, and 4). The mean VAS score was lower in a statistically significant way in Group PED compared to Group C and Group PE at the measurement points made during the 24th and 48th postoperative hours and discharge (P<0.05). The mean VAS score was similar in all groups during the first and third month (P>0.05). The mean VAS score was statistically significant superior in Group PED at the end of the 6th month. However, there was no statistical difference between the VAS scores and patient satisfaction scores of Group PE, for which we provided pre-emptive epidural analgesia, and Group C, to which we applied postoperative epidural analgesia.

In their study, which examined 111 cases that underwent thoracotomy, Tiippana et al. [14] applied thoracal epidural analgesia to 89 cases, iv-PCA to 18 cases and intramuscular opioid therapy to 4 cases. They evaluated the VAS scores of the cases in the 3rd and 6th

months after the discharge. They determined the chronic pain in 11% of the cases that had thoracal epidural analgesia and in 29% of those that had iv-PCA during the 3rd month. They reported chronic pain in 12% of the cases that had thoracal epidural analgesia and in 23% of the cases that had iv-PCA during the 6th month.

In the study conducted by Şentürk et al. [15] to examine the effect of 3 different analgesic techniques on the post-thoracotomy pain, 69 cases with thoracotomy were separated into 3 groups. Group 1 was given 0.1% bupivacaine and 0.1 mg morphine within 10 ml liquid 30 minutes before the anaesthesia induction in a bolus manner and the same solution was continued at a rate of 7 ml/h during the operation. Group 2, on the other hand, was given no medication during the preoperative and intraoperative period and the aforementioned solution was given during the postoperative period in a bolus manner. Group 3 was given PCA and morphine. As a consequence, it was observed that pain was lower in the group on which preoperative thoracal epidural analgesia was applied, compared to the other groups. Their query about pain, which was performed 6 months later, revealed that while the highest pain was in the group that had iv-PCA with the rate of 78%, the lowest pain was observed in the group that had preoperative thoracal epidural analgesia with the rate of 45%. Comparing the group that was given pre-emptive thoracal epidural analgesia with the group to which iv-PCA was applied, it was observed that the group that was given pre-emptive thoracal epidural analgesia had a statistically significant superiority; however, there was no statistical difference compared to the group that was given postoperative epidural analgesia. Therefore, they reported that preoperative thoracal epidural analgesia was a selectable method of preventing acute and long-term thoracotomy pain.

In their double-blind, randomised and prospective study including 60 cases, Can et al. [1] stated that even though pre-emptive, intraoperative or postoperative epidural analgesia was started on all cases, who were about to undergo major thoracotomy operation and to whom thoracal epidural analgesia was applied, an effective analgesia was formed without the superiority of one over the other in alleviating postoperative acute pain. However, according to the results that were obtained at the end of the postoperative 6-month follow-up of the cases in terms of pain, it was stated that the pre-emptive application of the thoracal epidural analgesia before the incision for the purpose of preventing or decreasing chronic post-thoracotomy pain had no efficient superiority on the intraoperative or postoperative thoracal epidural analgesia.

Central sensitisation plays an important role in the interpretation of the clinical pain. Thus, it shall be necessary for hypersensitivity to be removed in order to alleviate the clinical pain. Therefore, starting from the perioperative period, the development of central sensitisation should be prevented. Various pre-emptive analgesia models have been tried for that purpose. Attention was attracted to the insufficient blocking of nociceptive stimulation by thoracal epidural analgesia and the necessity of blocking the humoral nociceptive stimulants in preventing chronic post-thoracotomy pain [16].

In this study, multimodal approach was used in order to decrease the central and peripheral sensitisation more efficiently. We provided the postoperative analgesia of all three groups with the thoracal epidural analgesia in the study. In addition, we gave preoperative and postoperative i.v. dexketoprofen to Group PED with a time interval of 12 hours. Upon the evaluation of VAS score and PSS score performed at the end of the 6th month, Group PED had a statistically significant superiority compared to Group C and Group PE. A protocol that is consisted of opioids, local anaesthetic agents and NSAIDs is required for the efficient treatment of chronic post-thoracotomy pain. It is required in order to conduct more diverse studies on the selection of dose of the drugs to be used and drug administration periods. Instead of using opioids, local anaesthetic agents and NSAIDs individually for the treatment of chronic post-thoracotomy pain, it is required to use these three groups of drugs together to achieve a maximum decrease in the pain intensity, and it should be kept in mind that the patient satisfaction should be maximised by continuing the preoperative and postoperative analgesia applications as well as the pain treatment with the application of preemptive analgesia.

As a consequence; it was observed in this study that pre-emptive intravenous dexketoprofen and thoracal epidural analgesia have no superi-

ority over the pre-emptive epidural analgesia and postoperative epidural analgesia in the postoperative early period (hour 0, 1 and 4) acute pain. According to the results that were obtained at the end of a six-month follow-up regarding the postoperative late period (hour 24 and 48 and discharge) acute pain; it was determined that the combined application of intravenous dexketoprofen and thoracal epidural analgesia has superiority on pre-emptive epidural analgesia and postoperative epidural analgesia in the prevention or decrease of the chronic post-thoracotomy pain with the multimodal approach; however, the preoperative or postoperative application of the thoracal epidural analgesia have no superiority over one another.

Conclusion

We believe that instead of preoperative, intraoperative or postoperative application, the combined analgesics with the multimodal approach such as i.v. NSAIDs, epidural local anaesthetic agents and opioids would be more effective in decreasing or preventing the chronic post-thoracotomy pain and the drugs would have maximum efficiency and minimal side effects.

Disclosure of conflict of interest

None.

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