ORIGINAL ARTICLE

Relation between neutrophil-to-lymphocyte ratio with epidural analgesia timing and thoracotomy pain

Relación entre la proporción neutrófilos/linfocitos con el momento de la analgesia epidural y el dolor de la toracotomía

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Abstract

Objective: *This study investigated the relationship of the pre-operative neutrophil/lymphocyte ratio (NLR) to the timing of epidural analgesia administration and post-operative acute and chronic pain in thoracotomy.* **Materials and methods:** *The study was conducted on 60 patients, with NLR ≥ 2 (Group A) and NLR < 2 (Group B). Each group was divided into subgroups pre-emptive analgesia (Group P) and control group (Group C). Epidural analgesic solution was administered as a bolus before the surgical incision in Group P and at the end of the operation in Group C. NRS was questioned postoperatively at the 2nd, 4th, 8th, 12th, 24th h, 1st, and 3rd months and also additional analgesic needs were recorded.* **Results:** *In Group A, the pain scores of the patients who received pre-emptive epidural analgesia were lower at the post-operative 2nd, 4th, and 8th h and analgesic consumption was less in the post-operative first 24 h.* **Conclusion:** *It was observed that pre-emptive epidural analgesia reduced pain levels and additional analgesic consumption in the acute post-operative period in patients with pre-operative NLR ≥ 2.*

Keywords: *Pre-emptive epidural analgesia. Neutrophil/lymphocyte ratio. Post-operative pain. Chronic pain.*

Resumen

Objetivo: *Este estudio investigó la relación de la relación neutrófilos/linfocitos (NLR) preoperatoria con el momento de la administración de la analgesia epidural y el dolor agudo y crónico posoperatorio en la toracotomía.* **Materiales y métodos:** *El estudio se realizó en 60 pacientes, como NLR ≥ 2 (Grupo A) y NLR < 2 (Grupo B). Cada grupo se dividió en subgrupos de analgesia preventiva (Grupo P) y grupo control (Grupo C). La solución analgésica epidural se administró en bolo antes de la incisión quirúrgica en el Grupo P y al final de la operación en el Grupo C. La NRS se cuestionó posoperatoriamente a las 2, 4, 8, 12, 24 horas, 1 y 3 meses también adicionales Se registraron las necesidades analgésicas.* **Resultados:** *En el Grupo A, los puntajes de dolor de los pacientes que recibieron analgesia epidural preventiva fueron menores a las 2, 4 y 8 horas postoperatorias y el consumo de analgésicos fue menor en las primeras 24 horas postoperatorias.* **Conclusión:** *Se observó que la analgesia epidural preventiva redujo los niveles de dolor y el consumo adicional de analgésicos en el postoperatorio agudo en pacientes con NLR preoperatorio ≥ 2.*

Palabras clave: *Analgesia epidural preventiva. Relación neutrófilos/linfocitos. Dolor posoperatorio. Dolor crónico.*

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Introduction

Post-operative pain is an acute type of pain that starts with surgical trauma and ends with wound healing. Prevention of post-operative pain is very important in terms of patient satisfaction and prevention of possible complications[1].

Thoracotomy is one of the surgical procedures in which post-operative pain is most common. Inadequate pain control after thoracic surgery, insufficient respiratory effort, inability to cough, and the development of atelectasis may cause thromboembolism due to decreased mobilization[2], cardiovascular side effects with increased catecholamine release, and lung infections such as pneumonia and bronchitis[3].

Inflammation triggered by surgery is one of the most important mechanisms of post-operative pain[4]. Neutrophil/lymphocyte ratio (NLR), a marker closely related to systemic inflammation, has been associated with post-operative edema and ecchymosis in rhinoplasty[5] and with post-operative wound infection in spinal surgery[6]. In addition, NLR has been used as a prognostic factor in various malignancies such as rectum[7], lung[8], and breast[9] cancers and as a diagnosis and response criterion in various diseases such as diabetes mellitus[10] and acute appendicitis[11].

Although NLR is used as a marker of inflammation in various diseases in the literature, studies investigating its effects on post-operative pain, which is closely related to acute inflammation, and its effectiveness in the timing of analgesia management are limited. The primary aim of this study is to evaluate the relationship of NLR, an inflammation marker in thoracic surgery, with the timing of epidural analgesia and, second, to investigate the relationship of NLR level with post-operative acute and chronic pain.

Materials and methods

A total of 60 patients between the ages of 18 and 75 years and in the ASA I-III risk group who underwent elective thoracotomy between March 2020 and June 2021 were included in the study. Patients with a body mass index (BMI) > 30 kg/m^2, those with local anesthetic or opioid allergy, those who continue to use opioids, those with active infections, those with neurological disease, abnormal coagulation tests, patients with renal or hepatic insufficiency, patients who used any medication for the diagnosis of chronic pain, could not cooperate, patients who had a previous thoracotomy, and patients who were unable to compare physical and verbal performance were excluded from the study.

One day before the operation, pre-anesthetic examinations of all patients were performed. Patients with suitable conditions for the study were informed about the study, and their written consent was received. The numeric rating scale (NRS) score was explained in detail to the patients to evaluate their acute and chronic post-operative pain levels. NLR, age, gender, weight, and ASA risk scores of the patients were recorded before the operation.

Electrocardiography (ECG), peripheral oxygen saturation (SpO_2), and non-invasive blood pressure monitoring were performed on the patients who were taken to the operating table. Thoracic epidural catheter T_{4-5} was inserted at the level of the intervertebral space. After IV administration of propofol (2-3 mg/kg) and fentanyl (2 μg/kg), muscle relaxation was achieved with IV rocuronium (0.6 mg/kg). All patients were intubated with an appropriately sized left double-lumen tube for one-lung ventilation. After the tube position was confirmed with a fiberoptic bronchoscope, mechanical ventilation was started. After the patients were placed in the lateral decubitus position for surgery, the tube position was confirmed again with a fiberoptic bronchoscope. Anesthesia was maintained with 50% O_2/air and 2% sevoflurane in both groups. Muscle relaxant maintenance was provided with an additional dose of 0.25 mg/kg rocuronium according to the neuromuscular monitoring response.

Patients were divided into two groups as NLR level above 2 (Group A) and NLR level below 2 (Group B). After the epidural catheter was inserted, an equal number of subgroups were differentiated into groups A and B, and a bolus of 0.25% bupivacaine 0.1 ml/kg was administered through the epidural catheter 20 min before the surgical incision in the group to be administered pre-emptive analgesia (Group P), and an infusion of 0.1% bupivacaine was started at a rate of 0.1 ml/kg/h for 48 h. In the control group (Group C), a bolus of 0.25% bupivacaine 0.1 ml/kg was administered through the epidural catheter 20 min before awakening, and an infusion of 0.1% bupivacaine at a rate of 0.1 ml/kg/h for 48 h was started. In Group C, intraoperative analgesia was provided with 0.1-0.25 mcg/kg/min remifentanil infusion. Intramuscular pethidine (Aldolan-Gerot®, LibaLab.) was given at a dose of 1 mg/kg to all patients with a post-operative NRS value above 3. If the pain did not decrease, intramuscular diclofenac 75 mg (Diclomec®, Abdi

İbrahim) was administered. Application time and doses were recorded. NRS and additional analgesia needs were recorded for all patients at the post-operative 2nd, 4th, 8th, 12th, and 24th h. In the 1st and 3rd months postoperatively, the patients were contacted by phone, and their NRS scores were recorded.

Statistics

SPSS for Windows 17.0 program was used for statistical analysis. Descriptive variables are given as median (minimum-maximum), mean ± SD, and, if needed, as % (frequency) values. The conformity of the data to the normal distribution was evaluated with the Shapiro–Wilk test. During the data analysis, cases with Chi-square and Mann–Whitney U test $p < 0.05$ were considered statistically significant. G Power 3.1.9.4 (HHU, Germany) program was used to calculate the sample size. Based on the study of Öner et al.[12], alpha error = 0.05, beta error = 0.20, and effect size 0.8, it was concluded that a total of 52 patients, at least 26 for each group, would be sufficient. However, considering possible data loss, a total of 60 patients were included in the study.

Results

There was no significant difference between the groups in terms of demographic data ($p > 0.05$) (Table 1). There was no significant difference in pain scores and analgesic consumption between the patient groups with and without pre-emptive epidural analgesia in the pre-operative NLR < 2 group (Table 2). However, in the group with pre-operative NLR ≥ 2, the pain scores of the patients who received pre-emptive epidural analgesia were lower at the post-operative 2nd, 4th, and 8th h (respectively, $p < 0.001$, $p = 0.005$, $p = 0.006$) (Table 3) compared to the patients who did not receive pre-emptive epidural analgesia. Analgesic consumption was less in the post-operative first 24 h ($p < 0.05$) (Table 3). It has been observed that pre-emptive epidural analgesia has no effect on the chronicity of pain in patients with both NLR ≥ 2 and NLR < 2 (Tables 2 and 3).

Discussion

Thoracotomy is considered the most painful of all surgical procedures and must be treated with effective analgesia. In addition to the surgical incision, damage to the ribs and intercostal nerves, cutting of the major muscles, and placement of the chest tube play a role in the formation of this pain. It has been reported that eliminating this pain is very important in increasing patient comfort and contributes to both rapid recoveries of respiratory functions and reduction of complications[13,14].

Table 1. Demographic data (min-max, mean ± SD, n [%])

	Group A (NLR ≥ 2) (n = 32)	Group B (NLR < 2) (n = 28)	p
Age	66 41-75	62 23-74	0.213
Gender (M/F)	24 (75)/8 (25)	25 (89)/3 (11)	0.472
BMI	24.8 21.9-29.1	24.7 20.3-29.4	0.779
ASA (I, II, III)	5 (16)/16 (50)/9 (34)	6 (22)/15 (53)/7 (25)	0.068
NLR	3.45 ± 2.84	1.45 ± 0.445	**< 0.0001**

p values in bolds are statistically significant at $p < 0.05$. NLR: neutrophil/lymphocyte ratio.

Some patients may be at greater risk for post-operative pain. Determining this risk or patient group will help establish the analgesia and anesthesia strategy. Identifying patients with this risk group, particularly in cases that may cause severe pain, such as post-thoracotomy pain, may help us prevent post-operative pain-related complications. Patients with high baseline inflammation, such as those with high NLR levels, can be included in this risk group for post-operative pain.

With this current study, we accepted our hypothesis that if we detect the pre-operative NLR level, a risk factor for post-thoracotomy pain, in advance, we can reduce the severity and chronicity of acute post-operative pain by making the timing of epidural analgesia correct.

In our study, we found that the NRS levels at the post-operative 2nd, 4th, and 8th h and the amount of additional analgesic consumed in the first 24 h post-operatively in the control group in pre-operative NLR ≥ 2 patients were higher than the group in which pre-emptive thoracic epidural analgesia was administered. However, there was no difference between the subgroups in terms of pain scores and analgesic consumption in patients with pre-operative NLR < 2. This has shown us that patients with pre-operative high NLR may benefit from pre-emptive thoracic epidural analgesia. However, we observed that pre-emptive thoracic epidural analgesia had no effect on the chronicity of post-thoracotomy pain in both NLR ≥ 2 and NLR < 2 patient groups.

Table 2. Comparison of the effects of epidural analgesia application times on post-operative NRS and analgesic consumption in patients with pre-operative NLR < 2

Pre-operative NLR < 2 (n: 28)	Group P (n: 14)		Group C (n: 14)		p
	Median	Min-Max	Median	Min-Max	
Post-operative 2nd h NRS	2	2-4	3	2-4	0.282
Post-operative 4th h NRS	2	1-3	1.5	1-3	0.953
Post-operative 8th h NRS	2	0-2	2	1-3	0.805
Post-operative 12th h NRS	1	0-2	1	0-2	0.700
Post-operative 24th h NRS	0	0-1	0	0-2	0.923
Post-operative 1st-month NRS	0	0-3	1	0-5	0.303
Post-operative 3rd-month NRS	0	0-3	1	0-4	0.361
Post-operative first 24 h Additional analgesic consumption					
Meperidine (mg)	40	0-50	50	30-60	0.123
Diclofenac (mg)	0	0-75	37.5	0-150	0.711

NLR: neutrophil/lymphocyte ratio.

Table 3. Comparison of the effects of epidural analgesia application times on post-operative NRS and analgesic consumption in patients with pre-operative NLR ≥ 2

Pre-operative NLR ≥ 2 (n: 32)	Group P (n: 16)		Group C (n: 16)		p
	Median	Min-Max	Median	Min-Max	
Post-operative 2nd h NRS	3	1-5	5	3-7	**< 0.001**
Post-operative 4th h NRS	3	0-5	4	1-6	**0.005**
Post-operative 8th h NRS	1	0-3	3	1-5	**0.006**
Post-operative 12th h NRS	1	0-3	1	0-3	0.945
Post-operative 24th h NRS	0	0-3	1	0-2	0.716
Post-operative 1st-month NRS	1	0-5	1	0-4	0.390
Post-operative 3rd-month NRS	0	0-3	0	0-5	0.737
Post-operative first 24 h Additional analgesic consumption					
Meperidine (mg)	40	0-60	85	30-100	**< 0.001**
Diclofenac (mg)	75	0-75	75	0-225	**0.014**

p values in bold are statistically significant at p < 0.05. NLR: neutrophil/lymphocyte ratio.

It has been shown that patients with high NLR levels have pre-operative widespread systemic inflammation and may experience more pain due to the altered inflammatory balance[8]. Many studies in the literature show the relationship between pre-operative NLR level and post-operative pain. It has been shown that post-operative analgesic need and pain scores are higher in patients with a pre-operative NLR level above two after orthognathic surgery[15], arthroscopic shoulder surgery[16], and thoracotomy[17]. In our study, we determined the threshold value for NLR as 2 while forming our groups in accordance with the literature. We found that pre-emptive analgesia reduced the amount of post-operative analgesic and decreased pain scores in patient groups with NLR levels above 2.

In another study on thoracotomy surgery, it has been suggested that epidural analgesia can be chosen in patients with high NLR[18]. In this study, we chose epidural analgesia as the method of analgesia; however, we have demonstrated that patients with high

basal inflammation levels, such as high NLR levels, are at greater risk and that pre-emptive epidural analgesia will make a difference in preventing post-operative pain in this risk group.

Pre-emptive analgesia is defined as the prevention of central sensitization by applying painkillers or methods before the causes of pain occur and, thus, the cessation of pain before it starts[19]. In studies investigating the effects of pre-emptive thoracic epidural analgesia on acute post-thoracotomy pain, lower post-operative pain scores and analgesic consumption were found in the pre-emptive epidural analgesia method[20,21]. However, none of these studies evaluated pre-operative NLR levels. In the study of Neustein et al., it was shown that the pain levels in the first 6 h were statistically lower in patients who underwent pre-emptive epidural analgesia in thoracic surgery. They did not detect a significant difference in pain scores after 6 h[22]. In our study, NRS scores in the first 8 h were statistically lower in patients who underwent pre-emptive analgesia, in line with the literature. However, we observed that this change was only in the patient group with NLR levels above 2. There was no significant difference in NRS scores at other hours, and more analgesic consumption was observed in this patient group.

Unlike our study, the study investigating the relationship between chronicity of post-operative pain and NLR in the literature was conducted in lumbar disc surgery. They examined VAS levels at 6 months post-operatively to assess pain. It was found that the pre-operative NLR level showed a positive correlation with the pain at the post-operative 6th month[23]. In our study, we evaluated the NRS levels at the 1st and 3rd months to evaluate the relationship between the pre-operative NLR level and chronic post-thoracotomy pain; however, we could not find a relationship between the pre-operative NLR level and the NRS values at the 1st and 3rd months. We thought that this difference was due to the different duration of evaluation of chronicity and the fact that pain evaluation is a subjective method.

There are some limitations in our study. The most important limitation is that there are factors that affect the inflammatory response to surgery other than pain. Since our study was a single-center study, the results are limited to a certain region. Therefore, multicenter studies with larger patient groups are needed. Although there are many methods for measuring post-operative pain since pain is a subjective symptom, our study is also limited by the lack of a precise and objective method for measuring pain.

As a result, in our study, we concluded that the pre-emptive epidural analgesia method has a high inflammatory activity, and the pre-operative NLR level of patients above 2 is suppressed with the pre-emptive analgesia method, and their pain is better controlled in the post-operative acute period. We observed that the post-operative pain level and analgesic consumption of patients with low inflammatory activity and a pre-operative NLR level below 2 did not change with the application of pre-emptive analgesia. Thus, we provided sufficient analgesia by minimizing the unnecessary use of local anesthetic and the dose of local anesthetic to reduce the side effects in pain management. We believe that the NLR level, one of the parameters with pre-operative inflammatory activity in thoracotomy surgeries, may guide our choice of pre-emptive epidural analgesia.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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