


## CLINICAL RESEARCH

### Efficacy of ultrasound-guided Transversus Abdominis Plane (TAP) block in inguinal hernia surgery and the immunomodulatory effects of proinflammatory cytokines: prospective, randomized, placebo-controlled study



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Received 4 March 2020; accepted 26 August 2020

Available online 3 February 2021

#### KEYWORDS

Immunomodulation;  
Pain control;  
Proinflammatory  
cytokines;  
Transversus  
abdominis plane  
block

#### Abstract

**Background:** Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ) and Interleukin-1 $\beta$  (IL-1 $\beta$ ) are among the cytokines released secondary to the surgical stress response. The objective of this study was to investigate the effect of a Transversus Abdominis Plane (TAP) block on postoperative pain and its immunomodulatory activity through proinflammatory cytokines.

**Methods:** TAP (study group; n = 40) or p-TAP (placebo group; n = 40). Patients in the TAP group underwent an Ultrasound (US) guided unilateral TAP block using 20-cc 0.5% bupivacaine solution. Patients in the p-TAP group underwent a sham block using 20-cc isotonic solution. The TNF- $\alpha$  and IL-1 $\beta$  levels were measured three times at preoperative hour-0 and postoperative hours 4 and 24. Visual Analog Scale (VAS) scores were recorded at 0-hours, 30-minutes, 4-hours, and 24-hours. Analgesic use within the first 24-hours following surgery was monitored.

**Results:** The postoperative VAS score was decreased in the TAP group at all time points (0, 4, and 24 hours), and the differences between groups were statistically significant ( $p < 0.001$  for all comparisons). In the TAP group, the TNF- $\alpha$  and IL-1 $\beta$  levels at 4 and 24 hours post operation were significantly lower than the preoperative levels ( $p < 0.001$  for all comparisons).

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*Conclusion:* The TAP block for pre-emptive analgesia enabled effective hemodynamic control during the intraoperative period, provided effective pain control in the postoperative period, and decreased inflammation and surgical stress due to the decreased levels of the proinflammatory cytokines TNF- $\alpha$  and IL-1 $\beta$  in the first postoperative 24 hours, indicating immunomodulatory effect.

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## Introduction

Autonomic endocrine, metabolic, and immunological responses to hazardous stimuli serve to establish and sustain homeostasis and are collectively called the stress response. This response usually results from major traumas, surgery, sepsis, starvation, infections, burns, and other painful events. The goal of the stress response is to mobilize energy stores, activate hypermetabolism and the cardiovascular system, and increase blood flow to vital organs, thus improving the chances for survival. However, during anesthesia and surgical intervention, these responses may be harmful due to the increased energy consumption and myocardial load. Therefore, management of the stress response may decrease postoperative morbidity and mortality.<sup>1</sup> The stress response to surgery is affected by several factors, including the extent and type of surgery, duration of the intervention, age of the patient, amount of intraoperative bleeding, level of postoperative pain, and type of anesthesia.<sup>2,3</sup> Excessive intraoperative stress may increase the hospitalization duration and associated costs.<sup>1</sup> Numerous studies have focused on suppressing the endocrine and metabolic responses caused by surgical stress with different anesthesia techniques. These studies have shown that various anesthesia techniques stimulate neuro-humoral, autonomic, and immunological changes through several pathophysiological mechanisms and thereby affect the stress response.<sup>4</sup> A decrease in perioperative stress plays an important role in accelerating recovery, decreasing the hospitalization duration, and reducing hospitalization costs.<sup>5</sup> Tumor Necrosis Factor-alpha (TNF- $\alpha$ ) and Interleukin-1 Beta (IL-1 $\beta$ ) are among the cytokines released in response to surgical stress. These two cytokines originate from macrophages. Both IL-1 $\beta$  and TNF- $\alpha$  stimulate several cell types and thus increase eicosanoid production and protease synthesis.<sup>5</sup>

Inguinal hernia is one of the most common diseases treated with surgery. Each year, approximately 20 million patients with inguinal hernia undergo surgery.<sup>6</sup> Among the most common factors emphasized in postsurgical care are promoting early mobilization and decreasing postoperative pain to improve the quality of life and facilitate an early return to active daily life. Several multimodal, pre-emptive analgesic methods have been used to achieve this goal.<sup>7-9</sup> The Transversus Abdominis Plane (TAP) block enables effective pain control in lower abdominal surgery during both the intraoperative and postoperative periods. TAP block significantly decreases resting pain scores and physical immobility

in the postoperative period. This analgesic method also decreases the need for opioid use. An appropriate implementation of the technique with a suitable volume of analgesic may provide pain control for 24–48 hours in the postoperative period. TAP block may be implemented using a blind approach, under Ultrasound (US) guidance, or with laparoscopic assistance.<sup>10-15</sup>

In this study, we implemented a US-guided TAP block in addition to spinal anesthesia to decrease early-stage postoperative pain in patients who underwent unilateral inguinal hernia repair, and we compared the results of the TAP block group with those for a placebo group. Our objective was to investigate the effect of the TAP block on postoperative pain and its immunomodulatory activity through proinflammatory cytokines.

## Material and methods

This randomized double-blind, prospective, placebo-controlled clinical study was conducted following the approval of the Ethics Committee for Clinical Trials at Ordu University (approval information: 26.10.2017; 2017/127). All patients were informed about the TAP block procedure, and written informed consent was obtained. This study was conducted in accordance with universal ethical principles and the Helsinki Declaration (rev. 7; 2013). Patients who underwent unilateral inguinal hernia repair with an open surgical technique between January 1, 2018, and December 31, 2019, who were between the ages of 18 and 65 years, who had an American Society of Anesthesiology (ASA) score of I, II or III, and who provided informed consent were included in the study. The exclusion criteria were as follows:

- Patients with an ASA score of IV;
- Patients with malignant pathology;
- Patients younger than 18 years or older than 65 years;
- Patients who refused regional anesthesia;
- Patients with known hypersensitivity to local anesthetics;
- Patients with an infection in the surgery site;
- Patients with an incarcerated inguinal hernia; and
- Patients with contraindications for regional anesthesia (platelet count <100.000 and INR > 1.4).

None of the patients received premedication. All patients were required to fast for 8 hours before surgery. All patients underwent routine standardized monitoring in the operating

room, including electrocardiogram, pulse oximetry, and non-invasive arterial pressure monitoring. Vascular access was established on both hands of the patients with 20G Intravenous (IV) cannulas. The IV cannula on the dorsal side of the right hand was used to draw blood, and the one on the left hand was used for fluid replacement. Patient hydration status was maintained with 0.9% NaCl solution (dose: 4 mL.kg<sup>-1</sup>). As soon as the patient was positioned on the operating table, blood samples were obtained from the right hand for the measurement of TNF- $\alpha$  and IL-1 $\beta$  levels. The first blood sample was taken at hour 0. The second and third samples were taken at postoperative hours 4 and 24. TNF- $\alpha$  and IL-1 $\beta$  were analyzed using ELISA.

Each patient undergoing surgery received IV administration of 0.07 mg.kg<sup>-1</sup> midazolam for sedation. A total of 80 patients were included in the study. Patients were randomized into two groups: TAP (study group; n=40) and p-TAP (placebo group; n=40). After suitable cleaning and sterilization of the injection site, spinal anesthesia was initiated with 12.5 mg hyperbaric bupivacaine (Buvasin® 0.5% Spinal Heavy, VEM ilaç, Turkey) at level L3–L4 or L2–L3 with the patient in a sitting position. For spinal anesthesia, a 25G Quincke spinal needle was used, and the anesthetic solution was injected via the intrathecal route after CSF flow was observed. After this procedure, patients were moved to a supine position, and a US-guided TAP block was implemented for pre-emptive analgesia. Patients in the TAP group received 20-cc isobaric bupivacaine, and those in the p-TAP group received 20-cc saline. To ensure appropriate blinding of experimental conditions, one anesthesiologist prepared the solutions, and a second administered the solutions without knowing whether the syringe held saline or bupivacaine. Patients were randomized into the two groups using a closed envelope technique. Different anesthesiologists performed the TAP blocks, followed up with the patients postoperatively and prepared the drug solutions. Patients also did not know whether they received drug or saline; therefore, our study was performed in a double-blind manner. Before the surgical intervention, the Petit triangle was palpated under sterile conditions to determine the block sites for a subcostal approach of the US-guided unilateral TAP block. The US probe was placed transverse to the abdomen and immobilized, then an incision of the skin, subdermal fat tissue, m. obliquus externus, m. obliquus internus, m. transversus abdominis, and peritoneum was made. Then, 20 mL 0.5% bupivacaine solution (Bupivacaine HCl; Marcaine® 0.5%, AstraZeneca, PLC, UK) was injected using an 80-mm 22G needle between the obliquus internus and transversus abdominis muscles. During this injection, the placement of the needle tip and the distribution of the injected solution were monitored visually. The unilateral TAP block was carried out under US guidance using the LOGIQ (KPI Healthcare, GE, USA) ultrasound device and an 80-mm US-visible peripheral neurostimulation needle (B Braun, Melsungen, Germany). During the intraoperative period, the patient's Heart Rate (HR) and Mean Arterial Pressure (MAP) were measured and recorded at 0, 30, and 60 minutes after the first incision at minute 0. The time of the first incision was taken as minute 0; HR and MAP were measured and recorded at 30 and 60 minutes after the first incision. First, a suitable US image was obtained with the linear probe over the iliac crest at the middle axillary line, and then the m. obliquus internus

was penetrated with the peripheral neurostimulation needle. Next, 20-cc local anesthetic solution (bupivacaine or saline) was injected over the fascia of the transversus abdominis under real-time imaging. The sensorial block level was determined by the caloric response, motor block level, and modified Bromage scale. Surgical intervention is acceptable after the sensorial block reaches the T6 dermatome level. The patient's age, height, weight, sex, operative duration, ASA score, and physical risk classification were recorded.

All patients were informed about the Visual Analog Scale (VAS) before they left the operating room. The patients' pain scores and comfort levels were monitored during the first 24 hours postoperation. If the VAS score was 4 or more, 50 mg dexketoprofen IV was administered. The amount of dexketoprofen (mg) administered in the 24-hour period was recorded. During the first 24 hours postoperatively, VAS scores, the amounts (mg) of analgesic (dexketoprofen) administered, and the occurrence of complications (nausea, vomiting, hypotension, respiratory depression, sedation, itching, etc.) were monitored and recorded. Pain scores were recorded at 0 and 30 minutes in the postanesthesia care unit and again at 4 and 24 hours postoperatively.

## Power analysis

To determine the sample size for the power analysis, a table from "Determination of sample size in experimental studies where *t*-test was applied" was used. Assuming that the difference between the experimental group and the control group will be 20%, a two-tailed alpha value of 0.05 was taken, the power was accepted as sufficient at 0.80, and the number of individuals to be included in the study group was decided. According to this (postoperative VAS score and postoperative analgesic consumption), a standardized effect size of 0.80 was accepted, a two-tailed  $\alpha = 0.05$  and  $\beta = 0.10$  was used, and the intersection of these points was found and indicated a sample size of 38 people, i.e., 40 people were required for a single group. Thus, 80 people were recruited for the experimental and control groups.<sup>11</sup>

## Statistical analysis

Statistical analysis was performed with the IBM SPSS v21.0 (SPSS Inc., Chicago, IL, USA) software package. Normal distribution was checked with the Kolmogorov-Smirnov test. Numerical variables with a normal distribution are expressed as the mean  $\pm$  standard deviation, and variables that are nonnormally distributed are expressed as the frequency (percentage). The intergroup differences were determined with Student's *t*-test. For comparisons between groups, repeated measures ANOVA was used when the normal distribution hypothesis was met. The relationships between the categorical variables were evaluated with Chi-Square analysis. For all analyses,  $p < 0.05$  was considered statistically significant.

## Results

Patients who were admitted to the Training and Research Hospital in the Medical Faculty at Ordu University for uni-

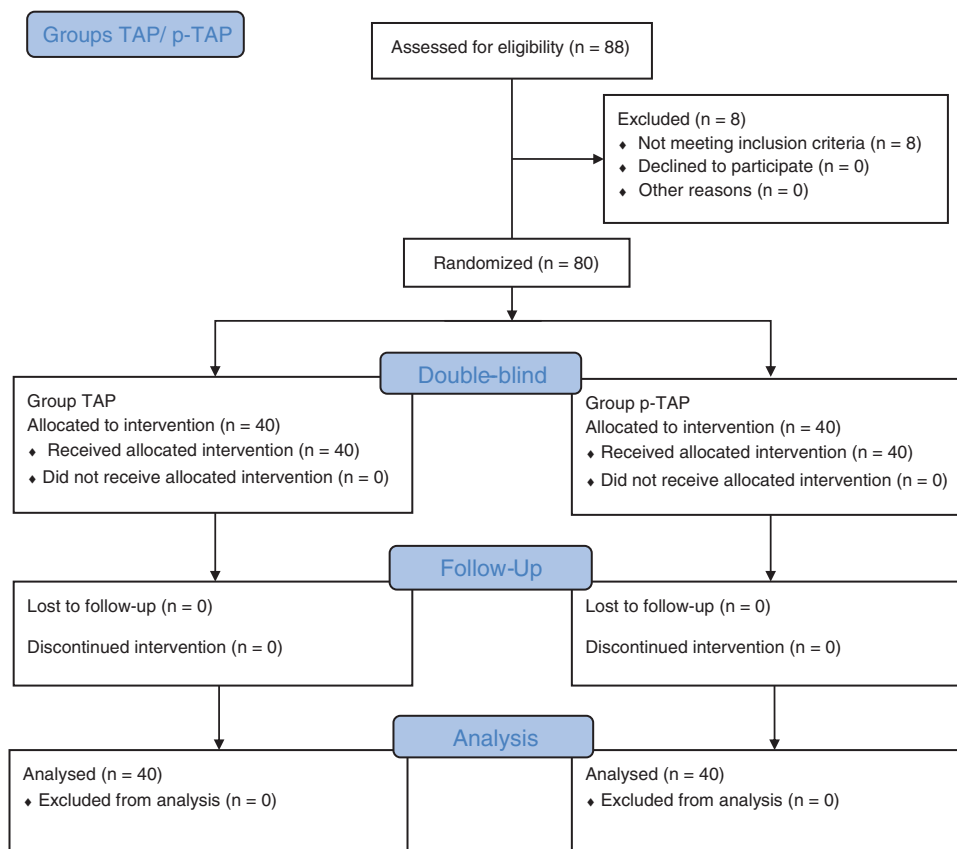


Figure 1 Participant flow diagram.



Figure 2 US image taken during the TAP block procedure.

lateral inguinal hernia repair were included in the study. A total of 80 patients who fulfilled the inclusion criteria of our study were randomized into two groups. The inclusion procedure is shown in Figure 1.

A sonographic image of one of the implemented TAP blocks is shown in Figure 2 and illustrates the proper placement of the needle. The distribution of patients according to sex is given in Table 1. No statistically significant differences

Table 1 Distribution of patients by sex.

Sex	TAP Group	p-TAP Group	p-value
Female	16	10	0.706
Male	24	30	
Total	40	40	

p-values were calculated by Student's *t*-test.

between the groups were found for sex or any other demographic characteristic ( $p > 0.05$ ). The demographic data are summarized in Table 2.

Although there was no statistically significant difference between the groups in intraoperative Mean Arterial Pressure (MAP) and Heart Rate (HR) at minute 0, we found there were significant differences in MAP at 30 and 60 minutes intraoperatively. This situation may be related to the low dose systemic absorption of 100 mg bupivacaine in the TAP block group and the cardiac depressant effect of bupivacaine (Tables 3 and 4).

The postoperative pain scores (VAS; 0–10) are summarized in Table 5. In the TAP group, VAS scores were low every time they were measured. Statistically significant differences between the groups were found at postoperative hour 0.30<sup>th</sup> minute at postoperative hours 4 and 24 (at all measurement time  $p < 0.001$ ). These findings confirmed that the TAP block provided very effective pain control. The groups showed no statistically significant difference in analgesic use (dexketoprofen consumption) in the first 24

**Table 2** Demographic characteristics of the study groups (mean  $\pm$  SD [min–max]).

	TAP Group (n = 40)	p-TAP Group (n = 40)	p-value
Age (year)	56 $\pm$ 10.44 (39–65)	51 $\pm$ 9.87 (38–64)	0.807
Weight (kg)	71 $\pm$ 21.56 (56–88)	69 $\pm$ 19.86 (51–81)	0.507
Height (cm)	150 $\pm$ 27.34 (148–180)	153 $\pm$ 21.46 (150–182)	0.656
ASA (I/II/III)	13/20/7	12/18/10	1.00

p-values were calculated by Student's *t*-test.

**Table 3** The change in intraoperative mean arterial pressure according to the groups (mmHg, n, mean  $\pm$  SD).

MAP	TAP Group (n = 40)	p-TAP Group (n = 40)	p-value
Intraoperative min 0	103.72 $\pm$ 15.99	96.29 $\pm$ 16.30	0.308
Intraoperative min 30	82.08 $\pm$ 12.46	89.92 $\pm$ 13.84	0.032 <sup>a</sup>
Intraoperative min 60	73.77 $\pm$ 11.19	78.16 $\pm$ 9.46	0.024 <sup>a</sup>

MAP, Mean Arterial Pressure.

p-values were calculated using one-way ANOVA.

<sup>a</sup>  $p < 0.05$ , statistically significant.

**Table 4** Change in intraoperative heart rate (HR: beats/min, mean  $\pm$  SD) according to group.

HR	TAP Group (n = 40)	p-TAP Group (n = 40)	p-value
Intraoperative min 0	81.32 $\pm$ 17.30	82.55 $\pm$ 14.86	0.406
Intraoperative min 30	70.28 $\pm$ 10.56	81.66 $\pm$ 16.79	0.027 <sup>a</sup>
Intraoperative min 60	68.67 $\pm$ 9.24	79.84 $\pm$ 15.30	0.021 <sup>a</sup>

The differences in Heart Rate (HR) between the groups were calculated using one-way ANOVA.

<sup>a</sup>  $p < 0.05$ , statistically significant.

**Table 5** Postoperative Visual Analog Scale (VAS) values (n, min–max, mean  $\pm$  SD).

VAS (0-10)	TAP Group (n = 40)	p-TAP Group (n = 40)	p-value
0 min (recovery)	2 (0–6) 2.16 $\pm$ 1.43	7 (4–8) 6.56 $\pm$ 0.92	$p < 0.001^b$
30 min (recovery)	3 (0–5) 2.68 $\pm$ 1.38	5 (4–7) 5.44 $\pm$ 0.82	$p < 0.001^b$
Postoperative hour 4	1 (0–3) 1.08 $\pm$ 1.04	4 (1–5) 3.8 $\pm$ 0.86	$p < 0.001^b$
Postoperative hour 24	1 (0–3) 1.16 $\pm$ 1.03	2 (0–7) 1.88 $\pm$ 1.30	0.039 <sup>a</sup>
Analgesic use (mg) in the first 24 h after surgery	50 $\pm$ 12.5 (25–100)	75 $\pm$ 25 (50–150)	0.06

p-values were calculated using the Chi-Square test for comparative analysis between the groups.

VAS, Visual Analog Scale.

<sup>a</sup>  $p < 0.05$ , statistically significant.

<sup>b</sup>  $p < 0.001$ , statistically significant.

hours after the operation ( $p = 0.06$ ). During the 24-hour postoperative monitoring period, none of the patients experienced any complications. The comparison between groups of the TNF- $\alpha$  and IL-1 $\beta$  levels showed no statistically significant differences between the preoperative measurements, whereas the levels of these proinflammatory cytokines were decreased at postoperative hours 4 and 24 in the TAP group. In the TAP group, the TNF- $\alpha$  and IL-1 $\beta$  levels at 0-hour (preoperatively level) were not statistically significant ( $p$ -values respectively  $p = 0.304$ ,  $p = 0.507$ ). In the TAP group, the TNF- $\alpha$  and IL-1 $\beta$  levels at 4 and 24 hours postoperatively were significantly lower compared to preoperative levels

( $p < 0.001$  and  $p < 0.001$ ;  $p < 0.001$  and  $p < 0.001$ , respectively). This finding indicated that TAP block decreased surgical stress, reduced the stress response to trauma, and had a positive effect on immunomodulatory activity. The TNF- $\alpha$  and IL-1 $\beta$  levels of the groups are shown in [Table 6](#).

## Discussion

Intraoperative hemodynamic values were lower in the TAP group than in the placebo group, and the postoperative VAS scores were lower in the TAP group than in the placebo group

**Table 6** Preoperative and postoperative TNF- $\alpha$  and IL-1 $\beta$  levels (n, min–max, mean  $\pm$  SD).

	TAP Group (n = 40)	p-TAP Group (n = 40)	p-value
Preoperative TNF- $\alpha$	118.872 $\pm$ 117.335 (13.333–564)	120.789 $\pm$ 56.33 (14–571)	$p = 0.304$
Preoperative IL-1 $\beta$	54.89 $\pm$ 23.87 (28.01–206.54)	55.75 $\pm$ 13.89 (25.47–209.13)	$p = 0.507$
Postoperative hour 4 TNF- $\alpha$	105.461 $\pm$ 76.045 (4–297.33)	116.65 $\pm$ 71.17 (15.5–601)	$p < 0.001^a$
Postoperative hour 4 IL-1 $\beta$	42.391 $\pm$ 27.825 (15.969–168.161)	56.79 $\pm$ 27.74 (24.255–201.12)	$p < 0.001^b$
Postoperative hour 24 TNF- $\alpha$	97.78 $\pm$ 71.03 (15.03–241.39)	117.589 $\pm$ 66.23 (17–619)	$p < 0.001^b$
Postoperative hour 24 IL-1 $\beta$	31.325 $\pm$ 12.667 (4.394–52.29)	44.25 $\pm$ 29.98 (36.76–192.35)	$p < 0.001^b$

p-values were calculated using one-way repeated measures ANOVA.

<sup>a</sup>  $p < 0.05$ , statistically significant.

<sup>b</sup>  $p < 0.001$ , statistically significant.

at all time points. Furthermore, at all time points, the postoperative proinflammatory cytokine (TNF- $\alpha$  and IL-1 $\beta$ ) levels relative to the preoperative levels were lower in the TAP group than in the placebo group. These results confirmed that TAP block enabled significantly effective postoperative analgesia and decreased surgical stress and proinflammatory cytokine levels, indicating immunomodulatory activity.

Özdilek et al.<sup>11</sup> divided 80 patients undergoing percutaneous nephrolithotomy into two groups. Forty patients underwent a US-guided subcostal TAP block, and the remaining 40 patients received IV paracetamol. The authors found that postoperative morphine consumption was lower in the US-guided TAP block group. Consistent with our results, they concluded that TAP block was an effective alternative to postoperative analgesia.

The results of a study conducted by Liu et al.<sup>16</sup> were also consistent with ours. These authors divided 65 patients who had undergone surgery due to gastric cancer into two groups. The first group underwent only general anesthesia, and the second group additionally underwent a TAP block. Blood levels of cortisol, epinephrine, norepinephrine, glucose, IL-10, and IL-6 were measured in the intraoperative and postoperative periods. The results showed that TAP block reduced the neuroendocrine stress response. The blood levels of cortisol, epinephrine, norepinephrine, glucose, IL-10, and IL-6 in the first 48 hours of the postoperative period were lower in the TAP block group than in the control group. The authors determined that TAP block had a positive role in immunomodulation and was effective in the management of perioperative hemodynamics.

Flaherty et al.<sup>17</sup> conducted a placebo-controlled double-blind study focused on open inguinal hernia repair and divided patients into two groups, a TAP block and a subcutaneous sham group, as in the current study. They determined that the 48-hour consumption of oxycodone (an analgesic agent) was not different between the TAP block group and sham block group. In our study, no difference was found between analgesic consumption in the placebo group and TAP block group. In our study, as in the study by Flaherty et al.,<sup>17</sup> our VAS scores were low in the TAP block group, and there was a significant difference between the VAS scores of

the two groups. Our results are in full agreement with the results of Flaherty et al.<sup>17</sup>

Vaillant et al.<sup>18</sup> induced rheumatoid arthritis in rats and investigated the effects of intra-articular ozone application on the proinflammatory mediators TNF- $\alpha$  and IL-1 $\beta$ . At the end of the experiment, they also evaluated the levels of nitric oxide and oxidative stress in splenic homogenates. The results showed that ozone treatment improved articular damage and lowered the TNF- $\alpha$  concentration and TNF- $\alpha$  and IL-1 $\beta$  mRNA levels. However, the NO (Nitric Oxide) levels remained unchanged.<sup>18</sup> In our study, the TNF- $\alpha$  and IL-1 $\beta$  levels, which are indicators of inflammation, were decreased in the TAP block group, similar to the decrease in these cytokines via the anti-inflammatory activity of ozone therapy. We suggest that TAP block creates an anti-inflammatory effect. The agreement between our results and those of this study also supports our hypothesis.

Xing et al.<sup>19</sup> induced renal ischemia in rats and investigated the protective effects of preoperative ozone therapy against ischemic injury. The results of the experiment showed less renal damage in rats that underwent ozone therapy. Additionally, the increase in the mRNA levels of the 55 proinflammatory mediators (including TNF- $\alpha$ , IL-1 $\beta$ , ICAM-1, and MPC-1) was inhibited.<sup>19</sup>

Our study has some limitations. Postoperative pain was monitored only for 24 hours. Due to the limited number of beds in our hospital, rapid discharge is important; however, pain management over 48 hours may be a better measure. However, we observed a near-significant decrease in analgesic consumption in the first 24 hours after the operation. We might have obtained significant results if we had been able to prolong the analysis of postoperative pain control to 48 hours.

In conclusion, a TAP block implemented for pre-emptive analgesia enabled effective intraoperative hemodynamic control, postoperative pain control, and decreased surgical stress as measured by decreased levels of TNF- $\alpha$  and IL-1 $\beta$  indicating an immunomodulatory effect in the first 24 hours after surgery. With this study, we confirmed once again the superiority of regional anesthesia techniques. Anesthesiology is not limited to putting patients to sleep and waking

them but is a much more comprehensive scientific discipline that addresses immunomodulatory interactions with significant potential for improvement in patients' quality of life.

### Ethics committee approval

Clinical Studies Ethics Committee of Ordu University, Faculty of Medicine, Decision n° 2017/127 Date: 26.10.2017.

### Informed consent

Written informed consent was obtained from patients who participated in this study.

### Conflicts of interest

The authors declare no conflicts of interest.

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