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Research Article

Evaluation of the Effect of Transversus Abdominis Plane (TAP) Block on Post-Laparoscopic Cholecystectomy Stress Responses: A Randomized Controlled Trial

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ABSTRACT

Background: The term "surgical stress response" refers to the physiologic response to surgery. The study aimed to evaluate effects of transversus abdominal plane (TAP) block on post-surgical stress responses.

Methods: This is a randomized, parallel-group clinical trial consisting of 60 patients undergoing laparoscopic cholecystectomy. Participants were randomized into two groups receiving either general anesthesia or general anesthesia plus TAP block. Blood samples for stress responses evaluating were obtained before anesthesia induction, 6 hours after extubation, and 24 hours after surgery termination. Pain levels were assessed after discharge from the recovery room and at intervals of 6, 12, and 24 hours after surgery.

Results: The trend in mean levels of blood sugar, cortisol, and WBC in each group was significant in the course of 24 hours. The mean levels of blood sugar and CRP was not significantly different between two groups; however, serum cortisol and WBC levels were different. Moreover, levels of IL-1 at 6 and 24 hours after surgery were significantly lower in the TAP block group. In Spearman's rank-order correlation analysis, age, BMI, pain level, cortisol, baseline IL-1, and TNF-α level had a significant linear correlation with IL-1 levels. There was a significant difference in pain scores between the two groups at 6 and 12 hours; however, at 24 hours, the difference was not statistically significant. The mean opioid consumption was significantly lower in the TAP block group.

Conclusion: This study showed the remarkable effects of TAP block on stress responses and pain scores.

Understandings of the surgical stress response have grown since Cuthbertson explained it in lower-limb injury [1]. Surgical stress response is the physiologic response to surgery and the name given to the hormonal and metabolic changes that follow surgery [2]. It has three key components: 1) sympathetic nervous system activation, 2) endocrine response with pituitary hormone secretion and insulin resistance, and 3) immunologic and hematologic changes including cytokine production, acute phase reaction, neutrophil leukocytosis, and lymphocyte proliferation [2].

During the past few decades, there has been a tremendous reduction in morbidity and mortality due to increased knowledge and understanding of the pathophysiology and optimization of the inflammatory and stress response mediators by different pharmacologic and procedural interventions [1].

More efficacious analgesia and modulating stress responses mediators result in faster recovery times and

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functional recovery, improved perioperative management, and decreased complications [3].

Transversus Abdominis Plane (TAP) block has recently been introduced as a postoperative pain control modality to reduce the dosage of opioids and their side effects [4-5].

Almost two decades have been passed since Rafi`s invention in 2001, yet an important question still remains [4]: As a component of multimodal analgesia, does TAP block modulate the stress response mediators? We hypothesize that better postoperative pain control with TAP block reduces the sympathoadrenal, endocrine, and cytokine responses and their markers such as WBC, blood sugar, TNF-α, IL-1, and serum cortisol level. It has been shown that following surgery, the main secreted cytokines are IL1, IL6, and TNF α [6-7]. Thus, the percentage of reduction in serum IL-1 levels was considered as the primary outcome.

Methods

Trial setting and design

A single-center, randomized, parallel-group clinical trial was conducted over the one-year period from March 2013 to March 2014 at Shariati Hospital, Tehran (affiliated with Tehran University of Medical Sciences). Written informed consent was obtained from each patient after a complete description of the procedures and illustration of the purpose of the study. The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences and registered in the Iranian Registry of Clinical Trials (IRCT201401255140N13).

Participants

Participants were selected from among patients undergoing laparoscopic cholecystectomy. To be included, the patients needed to be between 18 and 50 years of age and have a BMI of less than 30.

Other inclusion criteria were ASA class of 1 or 2 and a negative history of tobacco and/or other illegal drug abuse. Patients who had a history of receiving corticosteroids or immunosuppressive agents were not included in the study. Patients were excluded from the study if there were any contraindications for the intervention, either general anesthesia or TAP block, or if they had comorbidities such as severe cardiac, pulmonary, renal, or hepatic disease. Moreover, patients were excluded if the block procedure was not successful, if any complication was encountered during surgery, or if the operation lasted for more than two hours.

Interventions

The patients who entered the study were randomized blindly into two parallel groups. On arrival in the operation room, an intravenous (IV) access (with 20-gauge cannula) was established and secured; standard monitoring, including electrocardiogram (ECG), respiratory rate (RR), heart rate (HR), pulse oximetry (SpO2), and non-invasive blood pressure (NIBP), was applied; and the baseline vital parameters were recorded. Each patient was hydrated using 5 mL.kg-1 of normal saline IV solution. In both groups, patients were hydrated with 5 mL.kg-1 lactated Ringer's solution. Then anesthesia was induced by sodium thiopental 5 mg.kg-1 IV. Fentanyl 2µg.kg-1 IV and lidocaine 1.5 mg.kg-1 IV were injected as induction supplements. Tracheal intubation was facilitated by atracurium 0.5 mg.kg-1 IV. After five minutes, patients were intubated with an appropriate size, cuffed endotracheal tube (ETT). The ETT was fixed after hearing symmetrical lung sounds and ensuring the proper positioning of the tube. Then it was attached to a ventilator, and ventilation was begun in CMV mode. Isoflurane gas (concentration of 0.8-1.5%) was used for maintenance of anesthesia to maintain the cerebral state index (CSI) between 40 and 50.

In the TAP block + GA group, unilateral ultrasound-guided TAP block was done before starting the operation using 20 mL of bupivacaine 0.5%. Under sterile precautions, a high-frequency linear ultrasound probe was placed in the transverse plane in the space between the iliac crest and the subcostal margin. Abdominal wall layers (external oblique muscle [EOM], internal oblique muscle [IOM], transversus abdominis muscle [TAM], and their fascia) were visualized. Then, a 23-gouge needle was inserted between the EOM and IOM and proceeded to the space between the aponeurosis of the IOM and TAM under ultrasound guidance. Finally, bupivacaine was injected with intermittent aspiration, and local anesthetic spread was seen as a hypoechoic, oval-shaped shadow between the aponeurosis of the IOM and TAM.

In the general anesthesia group, no block was done.

The success rate of the block procedure was assessed 1) objectively by sedimenting the anesthetic (bupivacaine) between the IOM and TAM layers which were determined by means of ultrasound (Kayak sign); and 2) subjectively by assessing sensation at the site of the block in epigastric, periumbilical, and inguinal regions after the patient woke up in recovery.

Patients in the second group underwent general anesthesia in a similar way to the first group without administration of a TAP block. Patients in the GA group did not receive any additional approach to prevent postoperative pain before the end of surgery.

Patient awareness occurs in nearly 0.1% of surgeries because of inadequate anesthesia, and such a situation can augment the stress response in patients by stimulating the sympathetic system and increasing catecholamine release. With that in mind, the depth of anesthesia (using CSI) was monitored in both groups to maintain adequate depth of anesthesia, and CSI was kept between 40 and 50.

Following intraperitoneal gas insufflation, intraperitoneal pressure was kept between 12-15 mmHg. According to our surgery department, no gas aspiration,

wound infiltration, or intraperitoneal saline irrigation was done at the end of the procedure.

After termination of surgery, anesthesia was reversed by the administration of neostigmine 70 µg.kg-1 plus atropine 20 µg kg-1, and patients were extubated and transferred to the recovery room while fully awake. Patients were then transferred to the post-anesthetic care unit (PACU). An analgesic regimen with a PCA device was started following 40 µg/kg IV morphine loading dose if the Numeric Rating Scale (NRS) for pain was more than 3 (in the PACU or the ward). Each PCA device was filled with 30 mg morphine sulfate in 30 mL of saline 0.9% and was set to deliver a bolus dose of 1 mg of morphine sulfate with a lockout time of 15 minutes, with no preset of maximum dose or basal infusion rate. In the case of nausea or vomiting, ondansetron 4 mg IV was administrated. In the ward, if a patient reported NRS more than while using the PCA pump, Paracetamol 1 gr IV was infused.

Randomization and blinding

The participating patients were randomized into two groups of 30, each using a computer-generated random number table. Due to the nature of the intervention and our explanation about the procedure to patients before obtaining informed consent, the blinding of patients was not feasible; however, blinding was done in other parts of the study, including the observer evaluating pain levels and the amount of morphine given to the patient, the laboratory technician testing the blood samples, and the statistician analyzing the results.

Outcomes

In both groups, blood samples were obtained before anesthesia was induced, 6 hours after extubation, and 24 hours after termination of surgery, and the levels of IL1, white blood cells (WBCs), blood sugar, cortisol, C-reactive protein (CRP), and tumor necrosis factor-α (TNF-α) were measured.

In the postoperative period, pain ratings were measured by the NRS (0 = no pain, 10 = intolerable pain) just after discharging a patient from the recovery room and at intervals of 6, 12, and 24 hours. Twenty-four hours after discharge from recovery, patients' opioid usage was measured.

Sample size

Assuming a mean difference (MD) of 0.08 on IL-1 levels at the end of the operation, a standard deviation (SD) of 0.1, a power of 80%, a two-tailed significance level of 0.05, and a sample size of 24 was calculated for each group. Using this sample size, a mean difference (MD) of 0.6, an SD of 0.75, and the same power and significance levels of TNF-α were detected. With a prediction of a 20% rate of attrition, 30 patients were selected for each group (60 in total).

Statistical analysis

After data collection, IBM SPSS Statistic 22 (IBM Corporation, Armonk, NY, USA) was used to analyze it. Parametric statistical tests were used to analyze the data regarding the central limit theorem and the number of people in each group. The general linear model repeated measure was used to compare the quantitative data trends in each group and between the two groups in serial measurements. To compare the values from before and after surgery, the paired sample t-test was used, and to compare the values between the two groups, the independent sample t-test was used. A p-value <0.05 was considered statistically significant in all analyses.

2.8. Ethical considerations

The ethical principles laid out in the Declaration of Helsinki were complied with, and patients were free to participate in the study or not. The participants were assured that the information would be kept confidential and that they were free to withdraw from this trial and return to their standard procedure. In this study, no additional cost was imposed upon patients.

Results

In this randomized clinical trial, changes in the degrees of stress responses were compared in 60 patients undergoing elective laparoscopic cholecystectomy in Shariati Hospital who were randomly divided into two groups of 30 using general anesthesia (GA) alone or with TAP block.

A total of 64 patients who met the desirability criteria were selected and randomly allocated into the two groups. Thirty-two patients received GA and 32 received GA with TAP block. Ultimately, 60 patients (30 patients in each group) completed the trial (Figure 1). No significant differences were observed in the basic characteristics of subjects such as age, gender, and ASA group between the two groups (Table 1). However, levels of cortisol, CRP, IL-1, TNF-α, and pain score were significantly different between the two groups at baseline.

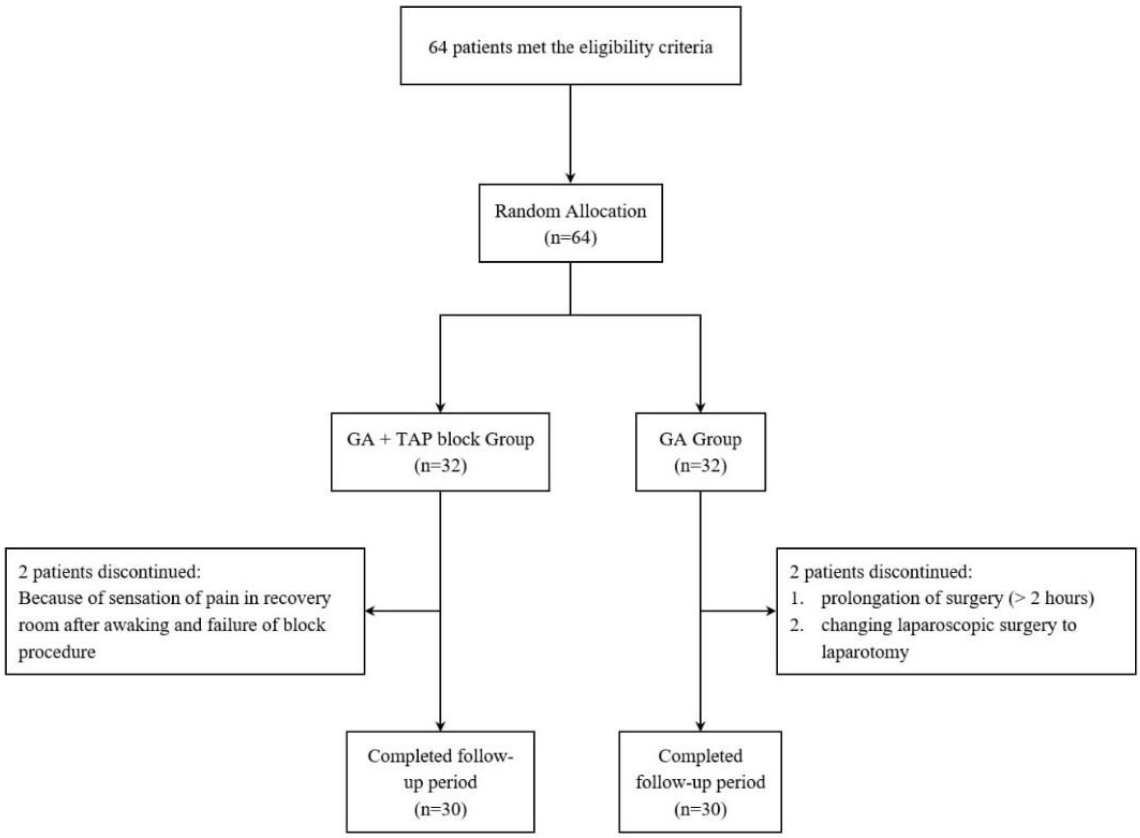
Table 1- Baseline characteristics of the patients.

Variable	GA Group (n=30)	GA + TAP Block Group (n=30)	P value
Sex, Female (%)[†*]	16 (53.3%)	14 (46.7%)	1
ASA Class, Class 1 (%)[†*]	19 (63.3%)	24 (80%)	0.15
Age, years, mean±SD[¥*]	45.63 ± 10.95	40.83 ± 12.14	0.11
Weight, kg, mean±SD[¥*]	72.57 ± 8.38	72.63 ± 10.23	0.98
BMI, $kg.m^2$, mean±SD[¥*]	22.83 ± 1.88	23.86 ± 2.09	0.05
Intraoperative Fentanyl (µg) mean±SD[¥*]	130.5±10.6	141.1±10.8	0.5

WBC, count/µL, mean±SD¥*	8007 ± 1715	7450 ± 2357	0.3
Blood Sugar, mg.dL^{-1}, mean±SD¥*	90.77 ± 8.35	96.76 ± 18.01	0.106
Cortisol, µg.dL^{-1}, mean±SD¥**	9.74 ± 18.01	8.23 ± 1.91	0.013
CRP, mg.L^{-1}, mean±SD¥**	9.97 ± 1.83	12.46 ± 4.80	0.011
IL-1, pg.mL^{-1}, mean±SD¥**	1.033 ± 0.563	0.700 ± 0.146	0.004
TNF-α, pg.mL^{-1}, mean±SD¥**	5.197 ± 0.960	4.713 ± 0.621	0.025
Pain, score, mean±SD¥**	2.4 ± 0.8	0.9 ± 0.7	<0.001

*There is no significant difference in groups
**There is a significant difference in groups
†Chi-square test
¥ Independent t test

Figure 1- Flowchart of the trial.



The trend of blood sample tests which were performed before, and 6, and 24 hours after the intervention was assessed in each group. It was shown that the trend in mean levels of blood sugar, cortisol, and WBC in each group was significant (p-value <0.05). This trend in CRP levels was significant only in the TAP block group. The differences in mean levels of blood sugar and CRP were not statistically significant between the two groups; however, serum cortisol and WBC levels were significantly different (Table 2).

Table 2- Changes in the mean levels of WBC, blood sugar, cortisol and CRP before surgery and 6 and 24 hours after surgery and comparing the trends between two groups.

Variable	Group	Before Surgery	After 6 hours	After 24 hours	P value (within group)	P value (between two groups)
WBC, count.µL^{-1}**	GA	8006.67 ± 1714.63	7263.33 ± 1351.50	6276.66 ± 1131.58	<0.001	0.009
	GA + TAP block	7449.67 ± 2356.81	6100.00 ± 1835.04	4686.67 ± 1588.70	<0.001	

Blood Sugar mg.dL^{-1}*	GA	90.77± 8.38	85.73± 10.23	86.97 ±5.70	0.002	0.19
	GA + TAP block	96.77 ± 11.86	89.53±14.52	89.73±13.87	0.001	
Cortisol, µg.dL^{-1}**	GA	9.74±2.59	15.28±2.84	14.78±3.36	<0.001	<0.001
	GA + TAP block	8.23±1.91	8.51±2.73	7.30±2.42	0.002	
CRP, mg.L^{-1}*	GA	9.97±1.83	8.97±2.70	9.40±3.42	0.2	0.85
	GA + TAP block	12.47±4.80	9.43±3.65	6.83±2.70	<0.001	

Δ Data are presented as mean±SD
*There is no significant difference in groups
**There is a significant difference in groups
General linear model repeated measure test

The IL-1 levels at 6 and 24 hours after surgery were significantly lower in the TAP block group compared to the GA group (p-value <0.001 for both 6 and 24 hours). Nevertheless, the IL-1 levels over the 24 hours were decremental in the TAP block group, whereas they increased in the GA group after 6 and 24 hours, which was significantly different from the TAP block group (p-value <0.001 for both) (Table 3).

Table 3- Changes in the mean levels of IL-1 before surgery and 6 and 24 hours after surgery and comparing the trends between two groups.

Variable		**GA Group (n=30)**	**GA+TAP Block Group (n=30)**	**P value (between two groups)**
After 6 hours**	Mean±SD	1.473±0.710	0630±0.121	<0.001
	Mean Difference from Baseline±SD	0.44±0.36	-0.07±0.18	<0.001
After 24 hours**	Mean±SD	1.510±0.617	0.600±0.001	<0.001
	Mean Difference from Baseline±SD	0.48±0.40	-0.10±0.15	<0.001
P-value** (within group)	-	<0.001	<0.001	-

**There is a significant difference in groups
General linear model repeated measure test

The levels of TNF-α were not significantly different between the two groups at 6 and 24 hours after surgery (p-value = 0.09 and p = 1, respectively); however, they decreased significantly over 24 hours (p-value = 0.025), although the decrement was not statistically significant at 6 hours (p-value = 0.073) (Table 4).

Table 4- Changes in the mean levels of TNF-α before surgery and 6 and 24 hours after surgery and comparing the trends between two groups.

Variable		**GA Group (n=30)**	**GA + TAP Block Group (n=30)**	**P value (between two groups)**
After 6 hours	Mean±SD	4.74±0.45	4.60±0.01	0.09
	Mean Difference from Baseline±SD*	-0.45±0.81	-0.11±0.62	0.073
After 24 hours	Mean±SD*	4.60±0.01	4.60±0.01	1
	Mean Difference from Baseline±SD**	-0.60±0.96	-0.11±0.62	0.025
P value (within group)	-	<0.001	0.37	-

*There is no significant difference in groups
**There is a significant difference in groups
General linear model repeated measure test

Pain scores (NRS) in the two groups were measured at 0, 6, 12, and 24 hours after surgery. A comparison of the values revealed a significant difference in pain scores between the two groups at 6 and 12 hours (p-value <0.001 for both); however, at 24 hours, the difference was not statistically significant (p-value = 0.276) (Table 5). The difference in the pain score at different hours of measurement was significantly different between the two groups compared to the baseline (p-value <0.001). The pain had an incremental trend in the TAP block group, whereas it initially increased and subsequently decreased

in the GA group. This observation can be justified, given the higher doses of opioids used in the GA group.

Table 5- Changes in the mean scores of pain intensity before surgery and 6, 12 and 24 hours after surgery and comparing the trends between two groups.

Variable		GA Group (n=30)	GA + TAP Block Group (n=30)	P value (between two groups)
After 6 hours	Mean±SD	5.0±1.0	1.5±0.5	<0.001
	Mean Difference from Baseline±SD	2.6±1.1	0.5±1.1	<0.001
After 12 hours	Mean±SD	4.6±1.0	2.0±0.6	<0.001
	Mean Difference from Baseline±SD**	2.2±1.2	1.1±0.9	<0.001
After 24 hours	Mean±SD*	3.6±0.5	3.9±1.2	0.276
	Mean Difference from Baseline±SD**	1.2±0.8	2.9±1.2	<0.001
P value (within group)*	-	<0.001	<0.001	-

*There is a significant difference in groups

**There is a significant difference in groups

General linear model repeated measure test

The means of opioid consumption 24 hours post-op in both groups were compared, and the results demonstrated that the mean dose of opioids used in the TAP block group was significantly lower than that of the GA group (29.87±4.17 in the GA group compared to 12.87±2.61 in the TAP block group; p-value <0.001).

Discussion

This study showed that in laparoscopic cholecystectomy, the use of a TAP block reduced IL1 serum levels. Furthermore, serum cortisol levels in the general anesthesia group were increased 6- and 24-hours following surgery. Considering these two factors as two important stress response indices, it can be concluded that the TAP block reduces the post-op stress response. There was a decrease in mean blood sugar, WBC, and TNF-α levels in the general anesthesia group. In contrast, the levels of parameters in serum other than TNF-α were significantly decreased in the TAP block group. The differences in the trend of changes in serum cortisol, WBC, IL-1, and TNF-α were significant. To the best of our knowledge, no previous study has compared these values in two groups like the present study.

The baseline levels of IL1 were not alike in the two groups, and it could induce a suspicion about the existence of a bias. Yet, to overcome this possible bias, the changes over time in IL1 levels in plasma in the two groups were compared.

The frequency of patients who experienced pain at an intensity greater than a score of 3 at 0, 6, and 12 hours after surgery was higher in the general anesthesia group than in the TAP block group. Yet, 24 hours following surgery, the frequency of pain score was the same in both groups. This observation was predictable due to the disappearance of the TAP block effect at this time. It should be noted that all patients in the general anesthesia group had a pain score higher than 3 at postoperative times. Also, 24 hours following surgery, patient opioid consumption was higher in the general anesthesia group than in the TAP block group. The need for postoperative morphine in patients undergoing cesarean section was significantly lower in the TAP block group compared to the placebo group [8]. In one study, patients with open appendectomy were divided into two groups: one group underwent standard care and the other group was TAP blocked with sonography with bupivacaine. Patients in the TAP block group clearly needed less morphine in the first 24 hours after surgery and also had less pain than patients in the other group [9]. The less need for postoperative opioid analgesics in TAP block patients has also been confirmed in other studies [10-12]. This effect of TAP block has also been demonstrated in patients after laparoscopic cholecystectomy and abdominal surgeries [13-14]. In another study on patients undergoing laparoscopic cholecystectomy (in two groups of bilateral TAP block and local anesthetic infiltration of trocar insertion sites), there was no significant difference in pain scores between the two groups at 4 hours and 24 hours after surgery. Therefore, it was concluded that postoperative pain in patients undergoing laparoscopic cholecystectomy was similar in the two groups [15]. A systematic review of RCTs that compared postoperative morphine consumption in TAP block patients and patients receiving placebo showed less morphine consumption, lower pain scores, and fewer opioid side effects [16]. In another study, TAP block in patients who were candidates for an ileostomy decreased post-op opioids consumption [17]. Another systematic review recommended that, although the TAP block's efficacy was shown to reduce pain and morphine consumption within the first 24 hours after surgery until definitive

reasons were determined, this method should not be substituted for routine performance [18]. A meta-analysis showed that a TAP block successfully reduced opioid requests in 24 hours after laparoscopic surgeries [19].

The main limitation of the current study was the kits for measuring serum levels of laboratory markers of stress responses. For this reason, qualitative variables had to be determined and qualitative analysis (values less than 0.6 pg.ml-1 for IL-1 and less than 4.6 pg.ml-1 for TNF-α) had to be used, which reduced the power of the study, limited defining other cut-off points of variables, and limited the use of complementary analyses such as the ROC curve. Also, despite the random division of patients into two groups, a number of items differed between the two groups - as seen in Table 1, and despite the analysis of trends in the two groups, it is recommended that future studies pay special attention to this. Furthermore, some studies have shown that profound neuromuscular blockage can reduce postoperative pain. In this study, the depth of neuromuscular blockage was not monitored; thus, if any significant difference in intensity of blockage was observed, this may affect postoperative pain intensity. Finally, sincere attempts were made to avoid producing any bias source in the study; however, there were some difficulties in blinding patients and the evaluator [20].

Conclusion

Overall, this study showed the remarkable effects of TAP block on patients' stress responses and pain scores compared to routine general anesthesia. TAP Block decreased stress response markers, pain scores, and the need for analgesic administration in the present clinical trial. It is recommended that further investigations be performed using quantitative measures of stress responses.

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