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RESEARCH ARTICLE / ARAŞTIRMA MAKALESİ

The effect of neuromuscular blockade depth, remnant CO2 excretion and prolonged assisted ventilation on postoperative pain in patients undergoing laparoscopic cholecystectomy; a prospective randomized, double-blind, clinical study

Laparoskopik kolesistektomi uygulanan hastalarda nöromüsküler blokaj derinliği, artık CO2 miktarı ve uzamış asiste ventilasyonun postoperatif ağrıya etkisi; prospektif, randomize, kontrollü çift kör klinik araştırma

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ABSTRACT

Aim: Laparoscopic cholecystectomy (LC) is a frequently applied in current practice. Pain management after LC is of great importance. In this study, the effect of neuromuscular blockade depth, remnant CO_2 excretion and prolonged assisted ventilation on postoperative pain in patients undergoing LC were evaluated.

Methods and Results: A total of 80 patients were taken to the study and divided into 4 groups. Group1: Control with standard LC, Group2: Receiving assisted ventilation in the Trendelenburg position for five minutes at the end of LC, Group3: Receiving deep muscle relaxation during the LC, Group4: Receiving deep muscle relaxation during the LC and taking assisted ventilation for five minutes at the end of LC. Postoperative period of 24 hours, the

evaluation of pain was done with visual analogue scale (VAS). In addition, nausea, vomiting, shoulder pain and surgical satisfaction were assessed.

As a result, 77.5% of the patients were female, the mean age was 51.9 ±12.5 (25-86) years. There was no statistically significant difference between the groups in terms of demographic data, nausea, and vomiting. The surgical duration (41.3±11.3 and 40.6±18.5min) and shoulder pain (75% and 80%) was found statistically significantly lower in Group 3 and 4 (P=0.035, P=0.002 respectively). In terms of comparing surgical satisfaction, it was found very high in Group 3 and 4 (P=0.001)

Conclusions: Deep muscle relaxation decreased postoperative shoulder pain, and it was found that assisted ventilation made for five minutes in the Trendelenburg position at the end of the LC reduced postoperative pain.

Key words: Pain, Postoperative, Laparoscopy, Cholecystectomy, Pain Management, Neuromuscular Blockade

ÖZET

Amaç: Laparoskopik cerrahi güncel pratikte sıkça uygulanan bir yöntemdir. Laparoskopik cerrahi sonrası ağrı yönetimi büyük önem taşımaktadır. Bu çalışmada nöromüsküler blokaj derinliğinin, remnant karbondioksit gazı atılımı ve uzamış asiste ventilasyonun, laparoskopik kolesistektomi geçiren hastalarda postoperatif ağrıya olan etkisi değerlendirildi.

Metot ve Bulgular: Laparoskopik kolesistektomi ameliyatı olacak toplam 80 hasta alındı. Hastalar 4 gruba ayrıldı. Grup 1: Standart laparoskopik kolesistektomi yapılan Kontrol grubu, Grup 2: Cerrahi bitiminde ek olarak trendelenburg pozisyonunda beş dakika asiste ventilasyon yapılan grup, Grup 3: Cerrahi süre boyunca derin kas gevşemesi yapılan grup, Grup 4: Cerrahi süre boyunca derin kas gevşemesi yapılan ve cerrahi bitiminde beş dakika boyunca asiste ventilasyon yapılan grup olarak belirlendi. Postoperatif 24 saat süre boyunca ağrı değerlendirilmesi visual analog scale (VAS) ile yapıldı. Buna ilaveten postoperatif bulantı kusma, omuz ağrısı varlığı ve cerrahi memnuniyet değerlendirildi. Hastaların %77.5 si kadın (n:62) cinsiyet, ortalama yaş 51.9±12.5 yıl (25-86) olarak bulundu. Vücut kitle indexi, anestezi risk skalası, bulantı kusma açısından gruplar arasında istatistiksel olarak fark saptanmadı. Cerrahi süresi ve ameliyat sonrası omuz ağrısı açısından yapılan karşılaştırmalarda, Grup 3 ve Grup 4'te ameliyat süresinin anlamlı derecede düşük olduğu (41.3±11.3 and 40.6±18.5 dakika) ayrıca omuz ağrısının (%75 ve %80) anlamlı derecede düşük olduğu görüldü sırasıyla P=0.035, P=0.002). Cerrahi memnuniyet grup 3ve 4'te anlamlı derecede yüksek bulundu (P=0.001).

Sonuç: Cerrahi koşulları iyileştirmek için derin kas gevşemesi yapmak postoperatif omuz ağrısını azaltmıştır ve cerrahi süre bitiminde Trendelenburg pozisyonunda yapılan beş dakika süre boyunca asiste ventilasyonun postoperatif ağrıyı azalttığı bulunmuştur.

Anahtar kelimeler: Ağrı, Postoperatif, Laparoskopi, Kolesistektomi, Ağrı tedavisi, Noromüsküler blokaj

INTRODUCTION

Compared to the traditional laparotomy, laparoscopic interventions reduce surgical trauma, speeding up postoperative healing and shortening the duration of hospital stay (1). Therefore, the use of laparoscopic interventions for many surgical procedures is becoming increasingly widespread. Nowadays, the laparoscopic approach to cholecystectomy has been a gold standard method (1). Although laparoscopic cholecystectomy is a minimally invasive intervention, patients often complain that postoperative pain is very severe (2, 3). This pain is usually reflected on the back and shoulders of the patient (4). During the pneumoperitoneum to ensure adequate visibility in laparoscopic operations, both the irritation of the used carbon dioxide gas to the intraabdominal structures and the pressure cause the pain. Studies indicated that as a result of the pneumoperitoneum pressure increased to 12-15 mm Hg, postoperative pain was more serious, and at low pressures, the pain was decreased significantly (4-6). On the other hand, in the surgical procedures performed at lower pressures to reduce pain, because adequate surgical field is often not provided, it is known to cause prolongation of the operation time and difficulty of the surgeon during the procedure (7).

Neuromuscular blockade is carried out to improve surgical conditions in all interventions to be performed with general Anesthesia. Proper muscle relaxation is provided in accordance with the property of the surgery and, if necessary, with the surgeon's demand. In the current Anesthesia practice, the depth of the muscle relaxant applied to the patient can be measured by various methods (8). One of them is carried out with devices that are placed in the peripheral muscle in the body and provide information through a monitor by working with the principles of accelomyography (8). In these devices, the degree of neuromuscular blockade is measured with the help of the abductor pollicis muscle. In the Train of Four (TOF) stimulation, the muscle relaxant effect may be decreased in the abdominal muscles and diaphragm even if there is no response in the muscles (9). For this reason, to ensure the depth, while continuous neuromuscular monitorization shows TOF 0, it can be determined that all muscles are paralytic in the range of 1-4 with the help of post tetanic count (PTC) (10).

The postoperative pain of patients having low laparoscopic inflation pressures with deep neuromuscular blockade has been investigated in studies so far (11). In this study, using low inflation pressure in laparoscopy due to deep neuromuscular blockade, the effect of it on postoperative pain of the patient was investigated, and at the end of the surgical period, the effect of residual carbon dioxide excretion on postoperative pain was investigated at the same time by facilitating the excretion of carbon dioxide by prolonged assisted ventilation for five minutes.

METHODS

Study Type

This is a prospective, randomized, double-blind, clinical study.

Subject Characteristics

This study is performed on patients who underwent elective laparoscopic cholecystectomy aged over 18 years old.

Ethics statement

The present study protocol was reviewed and approved by the Institutional Review Board of Hitit University School of Medicine (March, 16, 2016, approve no: /2016-0001). Informed consent was submitted by all subjects when they were enrolled.

Inclusion and exclusion criteria

A total of 80 patients who were scheduled for elective laparoscopic cholecystectomy, over 18 years of age, and whose Anesthesia risk score (ASA) was between 1-3 were included in the study. Patients with known neuromuscular disease, impaired liver or kidney function tests, allergies to any of the drugs used in the study, and patients who were undergone laparoscopic intervention then switched to open cholecystectomy, and patients who did not accept to participate were excluded from the study.

Study Design and Grouping Definitions

For the study design, the patients were divided into 4 groups. Group 1: Control group with standard laparoscopic cholecystectomy, Group 2: The group receiving assisted ventilation in the Trendelenburg position for five minutes at the end of the surgery, Group 3: The group receiving deep muscle relaxation during the surgical period, Group 4: The group receiving deep muscle relaxation during the surgical period and taking assisted ventilation for five minutes at the end of the surgery. The patients were assigned to the groups by computer randomization during the application. The contents of the groups were kept confidential from the surgeon performing the surgery and from the assistant performing the postoperative pain assessment. The minimum number of patients was calculated to be 20 in each group and 80 in total to obtain statistically comparable results.

Study measurements

During the interventions in all groups, a surgeon satisfaction questionnaire on the subject of the surgical field was employed. The questionnaire tried to determine whether optimal conditions were provided for surgery (very good, good, acceptable, and not suitable to work in these conditions). In all

patients, 100 mg/2 ml intravenous Tramadol was performed as standard during waking. After extubation, the patients were transferred to the service after normal follow-up values in the wake-up unit. Diclofenac Sodium two times/per day intramuscular was performed routinely for all patients who were taken to the service for postoperative analgesia needs. Pain monitoring of patients was made by the surgical assistant who did not know the groups at 1, 6, 12, 18, 24th hours after surgery. Visual Analogue Scale (VAS) was used in the evaluation of pain. Patients with analgesia requirements other than standard analgesia were noted. All patients were questioned for postoperative nausea, vomiting and shoulder pain.

Anesthesia and Surgical Procedures

After standard preoperative monitorization (electrocardiogram, blood pressure, pulse-oximetry, temperature), Anesthesia induction was started with 2.5 mg/kg Propofol and 1mcg/kg fentanyl. Neuromuscular monitorization was performed by calibrating through accelomyography before giving the muscle relaxant (TOF-Watch SX, version 2.5 INT 2007 Organon Ltd., Ireland). The arm to be used in the study was immobilized, the finger was connected to the accelomyography and the other arm was used during the operation. For facilitating intubation, 0.6 mg/kg Rocuronium was administered to all groups. Following the neuromuscular block, the patients were intubated with an endotracheal tube. Anesthesia was maintained with sevoflurane 2 minimum alveolar concentration (MAC) and 60% nitrogen (N_2O) and 40% oxygen (O_2) in a total of 2 liters of the gas mixture. In patients of Group 3 and 4 when TOF was 0, post tetanic count (PTC) was monitored. If the PTC was not in range 1-4, an additional dose of 0.3 mg/kg was given for the duration of the case. In Group 1 and 2, intubation started when TOF was 0, and the need for additional doses was determined according to the values of the TOF. For antibiotic prophylaxis, all patients were given 1 g of Cefazolin Na. Patients were operated after intubation.

In all patients, carbon dioxide (CO_2) insufflation was performed at 12 mmHg with veress needle as standard. Laparoscopic cholecystectomy was performed by the same senior surgeon with the standard 4 trocars. Patients in group 2 and group 4 were taken to the Trendelenburg position to make the assisted ventilation at the end of the surgical procedure, the 12 mm trocar in the umbilicus was left open to allow gas output, and assisted ventilation was continued for five minutes. After the procedure, the trocar was pulled out, and the fascia and skin were sutured. Patients were extubated when TOF was 90 and above, and in Groups 3 and 4, Sugammadex was administered in a dose of 2-8 mg/kg to the patients who could not remove the muscle relaxant.

Statistical analysis

The number of samples for the groups was calculated with power analysis (Power = 0.80) before starting the study. The PASS (Power Analysis and Sample Size Software, NCSS, LLC. Kaysville, Utah, USA) package software was used for power analysis (version 11-trial). To calculate the estimated number of samples to be used in the study, the hypothesis means were determined as 6, 5.5, 5 and 4, respectively, and the standard deviation was 1.5 for four groups with an equal number of subjects in each group similar to the studies in the literature. Alpha (α) was accepted as 0.05 (95% significance level). As a result of power analysis result, the sample number was determined as 20 for each group, as a total of 80, with the impact size of 0.373% and power of 81% (0.81).

In this study, statistical analyses were made using SPSS (Version 22.0, SPSS Inc., Chicago, IL, USA Hitit University licensed) package software. Descriptive statistics were presented as an average ± standard deviation for normal distributed continuous data, median (Min-max) for variables without normal distributed continuous data and with sequential (ordinal) data, and number and percentage (%) for variables with categorical data. The Normality distribution was examined by Kolmogorov-Smirnov and Shapiro-Wilk tests. The homogeneity of the variances was examined by Levene's test. For continuous variables, in the comparisons of two independent variables averages, independent sample T-test was used for data showing normal distribution, and the Mann-Whitney U test was used for data not showing normal distribution. Chi-Square test was used for nominal variables. More than two group comparisons were made by using variance analysis (ANOVA). Ordinal data (pain score) was assessed by the Kruskal-Wallis test. To determine which group the difference is sourced from, the binary comparisons were made with the Mann Whitney U test (post-hoc tests) following the Kruskal Wallis tests, taking into consideration the Bonferronni correction. The statistical significance level was accepted as $P<0.05$.

RESULTS

After the approve of ethical consent, a total of 80 patients who admitted to the general Surgery Clinic between 01 May 2016 and 01 December 2016 and accepted to participate in the study were assigned to the groups by table randomization method. Twenty patients were involved in each group. All patients were undergone laparoscopic cholecystectomy with standard equipment by the same senior surgeon. There was no conversion to open surgery and any bile duct injury in all groups.

All patients were successfully awaked by extubation and transferred to the service. No perioperative complications were developed.

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According to the demographic characteristics of the patients participating in the study, the distribution of the patients to the groups was seen to be homogeneous in terms of age, gender, and body mass index (BMI). Also, 77.5% of the patients were female (n: 62), 22.5% male, and the mean age was 51.9±12.5 years (25-86) (Table 1).

The average operation time in the study was 45 minutes (min: 15, max: 95). The surgical duration (41.3±11.3 and 40.6±18.5min) was found statistically significantly lower in Group 3 and 4 (*P*=0.035). No statistically significant difference was found between the groups in terms of nausea and vomiting. However, clinically significant nausea and vomiting were lower in Group 3 and 4 (*P*= 0.213) (Table 2). When the groups were evaluated in terms of postoperative shoulder pain, the pain was found to be significantly lower in Group 3 and 4 (*P*= 0.002) (Table 2).

All groups were postoperatively evaluated at 0, 3, 6, 12th hours after surgery with VAS score in terms of general pain. Postoperative 3rd and 6th hour values of VAS scores were significantly lower in Group 2 and 4 (*P*= 0.016, *P*=0.03, respectively) (Table 3). No statistically significant difference was found in the measurements performed at other times (*P*=0.076, *P*=0.185, *P*=0.207 respectively) (Figure1).

When the surgeon satisfaction was questioned during surgery, the surgeries of patients in Group 3 and 4 were found to be significantly more comfortable between all groups (*P*=0.001) (Table 4).

DISCUSSION

In laparoscopic surgical procedures, high pressures are generally preferred because carbon dioxide gas and abdominal inflation pressures provide better vision of the surgical area (6). High inflation pressures are known to improve surgical conditions, reduce lung capacity with increased intraabdominal pressure, and increase postoperative pain and anaesthesia complications (11). For this reason, increasing the depth of muscle relaxation can be an option to optimize the surgical conditions of operation using low inflation pressures. Therefore, the postoperative pain of patients may be thought to be reduced. Previously, Julia C. Radosa et al. showed that five-minute assisted ventilation reduced postoperative pain in the Trendelenburg position at the end of the surgical period (12). Similarly, in this study, the patient was taken to the Trendelenburg position at the end of the surgery, and the assisted ventilation prevented the inner residual gas. Although there was no statistically significant difference, postoperative VAS scores were found to be lower in groups 2 and 4, which may be clinically significant. Failure to statistically significant results can be explained by the limited sample size. There are studies indicating that the Trendelenburg position alone is adequate to facilitate

the remnant gas excretion and that the postoperative pain can just be reduced by this simple maneuver (13-15).

In addition to high inflation pressures, carbon dioxide gas is also known to cause postoperative pain, but carbon dioxide gas has not been fully clarified by which mechanism it causes postoperative pain. As is known, carbon dioxide gas is a peritoneal irritant, it is thought to cause pain with morphological and biochemical changes in the mesothelium. It is also known that carbon dioxide gas causes shoulder pain through C4 as a result of direct pressure effect to the phrenic nerve (16). Because of this theory, Sanhu et al. did not find a significant difference in postoperative shoulder pain in patients with low laparoscopic inflation pressures (17). Another study by Bogani et al. found that the incidence of shoulder pain was low in the group with low pressure (18). However, the incidence of postoperative pain was seen to be similar between the two groups. There was no significant difference between the groups in terms of postoperative analgesic requirements, which was reported by Bogani et al. and Sarli et al (18, 19). The authors indicated that working with low pressure reduced the surgical field and vision. They also suggested that these factors could cause organ injury and an increase in working time. At the end of the surgery, the pain of the patients with Trendelenburg was similar to the pain scale of the groups in which deep muscle relaxation was performed. In groups with deep muscle relaxation, shoulder pain, nausea, and vomiting were found to be lower. In connection with the subject, in this study, the incidence of shoulder pain, nausea, and vomiting in Group 3 and 4 with deep muscle relaxation is very low.

Jackson et al. proved that there was a direct relationship between pain severity and residual carbon dioxide after laparoscopy (20). In our study, postoperative pain severity decreased significantly in both groups (Group 2 and Group 4) where prolonged assisted ventilation was performed, and this shows the effect of assisted ventilation on residual carbon dioxide excretions.

In groups with deep muscle relaxation (Group 3 and Group 4), surgical satisfaction is more, which is also reflected in the intervention durations.

Previous neuromuscular monitorization studies examined the TOF values and indicated that adductor pollicis muscle relaxation did not fully reflect the abdominal muscles relaxation (21). For this reason, deep muscle relaxation was performed in patients of Group 3 and 4. In cases where the surgical time was short and the patient did not break down the muscle relaxant, *Sugammadex* was applied before the patient woke up. In laparoscopic surgery, deep muscle relaxation until pneumoperitoneum is terminated will make it difficult for the patient to wake up if it is considered that the reverse of neuromuscular block by acetylcholine esterase inhibitors at the end of the operation is weak and inadequate. The duration of the patients to break down the muscle relaxant may be variable, as well as,

be in connection with the surgical period. The reversing of *Rocuronium* block in the presence of PTC 1-2 by using 0.07 mg/kg neostigmine requires approximately 41 minutes while TOF is 80% (26-56 minutes). After the pneumoperitoneum is terminated, the average time to close the skin is about 15 minutes and rarely is prolonged, and patients wake up because to be not able to break down the muscle relaxant completely. For this reason, continuous maintenance of the deep block during laparoscopic surgery should be considered by only the clinicians with access to the *Sugammadex*.

Deep muscle relaxation resulted in shortened surgical period and increased surgical satisfaction. When comparing the groups 1-2 to the groups 3-4, the acceptable conditions for the surgeon were seen as superior. In studies with low laparoscopic inflation pressures, surgical conditions could not be optimised. In this study, our aim in ensuring deep muscle relaxation was to reduce the risk of surgical complications and increase patient comfort by reducing the patient's postoperative pain. However, the shortening of the anaesthesia period as a result of the shortening of the surgical period provides extra advantage for the method.

Study limitations

There some limitations for this study. However in all patients, carbon dioxide (CO_2) insufflation was performed at 12 mmHg with veress needle as standard, but the volume of abdominal cavity of the each patients differs. So all patients did not receive equal CO_2 gas volume. This situation may effect postoperative pain. In the other hand, patients' postoperative pain score was measured with visual analogue score. VAS score is not an objectively measurable score. Each person's pain threshold may be different. So this parameters may effect postoperative pain score.

CONCLUSION

As a result, this study showed that deep muscle relaxation to improve surgical conditions decreased postoperative shoulder pain and nausea-vomiting. In addition, during the five minutes at the end of the surgical period, the assisted ventilation was found to reduce postoperative pain even in the group without deep muscle relaxation. According to these results, in patients undergoing laparoscopic intervention, prolonged ventilation process would be beneficial as a routine procedure in patient groups that are thought to not show complications in the mentioned position.

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CONFLICT OF ONTEREST

The author declared she do not have anything to disclose regarding conflict of interest with respect to this manuscript. None declared.

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Figure 1.

Postoperative Visual analog scores (VAS) of patient's

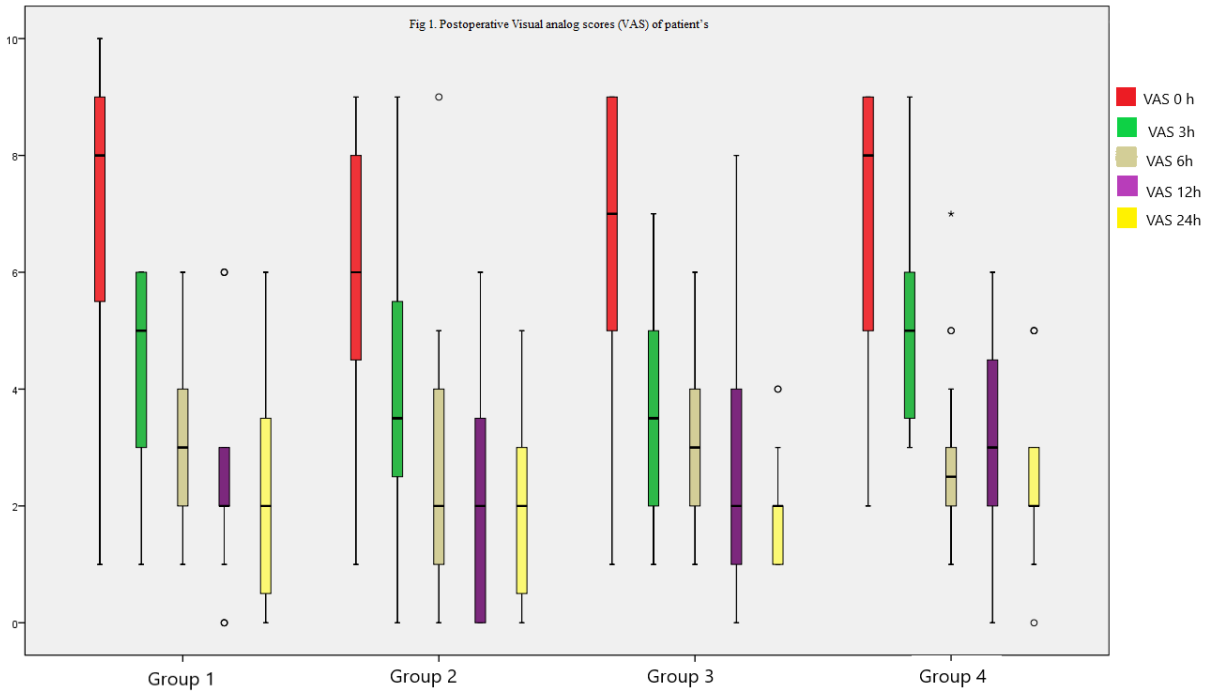

Table 1. Patients' characteristics

Age (mean ± [a]SD		51.9±12.5 (min:25-max:86)
BMI (mean ± SD)		30.3±5.4 (19.7-47.6)
		n (%)
Gender		
	Male	18 (22,5)
	Female	62 (77.5)
Sugammadex to awaken		
	Made	19 (23.8)
	Not made	61 (76.3)
Previous surgeries		
	No surgery at all	49 (61.3)
	Surgery on the upper abdomen	10 (12.5)
	Surgery in the lower abdomen	21 (26.3)
Diagnosis of Surgery		
	Cholecystitis with acute stones	10 (12.5)
	Cholecystitis with chronic stones	54 (67.5)
	Hydropic Swell	7 (8.8)
	Chronic Cholecystitis	9 (11.3)
Nausea, vomiting		
	Exist	51 (63.7)
	Not exist	29 (36.3)
Shoulder pain		
	Exist	56 (70)
	Not exist	24 (30)
Total		**80 (100)**

[a]SD: Standard deviation

Table 2. Comparison of groups in terms of nausea, vomiting and shoulder pain

			Nausea Vomiting		Total	*P*	Shoulder pain		Total	*P*
			Not exist	**Exist**			**Not exist**	**Exist**		
Patient Groups	**Control**	n	15	5	20	**0.213[a]**	13	7	20	**0.002[a]**
		%	75.0%	25.0%	100.0%		65.0%	35.0%	100.0%	
	Trendelenburg	n	14	6	20		14	6	20	
		%	70.0%	30.0%	100.0%		70.0%	30.0%	100.0%	
	Deep muscle relaxation	n	15	5	20		15	5	20	
		%	75.0%	25.0%	100.0%		75.0%	25.0%	100.0%	
	Deep Muscle Relaxation and Trendelenburg Position	n	16	4	20		16	4	20	
		%	80.0%	20.0%	100.0%		80.0%	20.0%	100.0%	
Total		n	60	20	80		58	22	80	
		%	75.0%	25.0%	100.0%		72.5%	27.5%	100.0%	

[a] Chi-square test

Table 3. Comparison of groups in terms of VAS (Visual Analog Scale) score

	Median (min-max)				
Time interval (hour)	**Control**	**Trendelenburg**	**Deep muscle relaxation**	**Deep Muscle Relaxation and Trendelenburg Position**	[a]**P value**
0	8 (1-10)	6 (1-8)	7 (1-9)	8 (2-9)	0.076
3	5 (1-7)	3.5 (0-9)	3.5 (1-7)	5 (3-9)	**0.016**
6	3 (1-6)	2 (0-9)	3 (1-6)	2.5 (1-7)	**0.003**
12	2 (0-6)	2 (0-6)	2 (0-8)	3 (0-6)	0.185
24	2 (0-6)	2 (0-5)	2 (1-4)	2 (0-5)	0.207

[a]Kruskal-Wallis test