VILNIUS UNIVERSITY

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COMPARISON OF GENERAL AND COMBINED ANESTHESIA DURING LAPAROSCOPIC COLORECTAL SURGERY

Summary of Doctoral Dissertation

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VILNIAUS UNIVERSITETAS

DIANA GASIŪNAITĖ

BENDROSIOS IR KOMBINUOTOS ANESTEZIJOS METODŲ PALYGINIMAS PACIENTAMS, KURIEMS ATLIEKAMOS STOROSIOS ŽARNOS LAPAROSKOPINĖS OPERACIJOS

Daktaro disertacijos santrauka

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LIST OF ABBREVIATIONS

ACTH – adrenocorticotropic hormone

APTT – activated partial thromboplastin time

ASA – physical status classification according to the American Association of Anesthesiologists

BMI – body mass index

BP – blood pressure

BSA - body surface area

Cdyn – the volume to which the lungs expand at a given pressure, dynamic compliance

CI – cardiac index

CMV – controlled mechanical ventilation

CO – cardiac output

CRP – C reactive protein

DBP– diastolic blood pressure

EA – epidural analgesia

EtCO2 – carbon dioxide concentration in exhaled gas

HPA – hypothalamic-pituitary-adrenal system

HR – heart rate

IAS − intra-abdominal pressure

IL-1 – interleukin-1

IL-6 – interleukin-6

MBP – mean arterial blood pressure

MV – minute ventilation volume

PaCO2 – partial carbon dioxide pressure in the blood

PAH – primary arterial hypertension

PIP – the maximum pressure of the air passages value during inhalation

Raw − airways resistance

SBP – systolic blood pressure

SD – standard deviation

SNS – the sympathetic nervous system

SPA – standardized prothrombin activity

SV – cardiac stroke volume

TNF-α − tumour necrosis factor α

VCO2 – carbon dioxide elimination

VAS – visual analogue scale

CONTENT

1. INTRODUCTION

In modern medical practice, we face the necessity of more rapid postoperative rehabilitation of patient. In scientific literature methodologies, complex measures of prospects and possibilities of enhanced recovery after surgery are being analysed. It is relevant to use the conventional anesthetic methods to laparoscopic colorectal surgery and the search for possibilities to patient's enhanced recovery after surgery. Laparoscopic surgery is associated with a smaller surgical incision and a shorter postoperative discomfort and pain in the area of operation, but postoperative pain management still remains a problem. Laparoscopic colorectal resection, even being a minimally invasive technique for laparoscopic surgery, stimulates the body's response to stress and inflammatory mediators, which is determined to be the same as in open operations. Perioperative stress can inhibit a proper adaptive immune response. The pneumoperitoneum in laparoscopic surgery increases the level of vasopressin and catecholamines. Hypercapnia and pneumoperitoneum stimulate the sympathetic nervous system and catecholamines release. By surgical stress induced hormones - catecholamines, ACTH, cortisol release during the autonomous nervous system and the HPA system are involved in suppression of the body's immune function (Vallejo R et al., 2003, Kelbel I, Weiss M, 2001). Both the proinflammatory cytokines−IL-1, IL-6 and TNF-α secreted by monocytes and macrophages, and lymphocytes activated by the surgical stress can stimulate the HPA system and the neuroendocrine system. Neuroendocrine system together with the pro- and anti-inflammatory cytokines, synergistically complement the perioperative immunosuppression. IL-6 not only controls the interaction of immune cells, but also affects pain and hypersensitivity associated with inflammation, neuropathy and cancer pain directly regulating the amount of pain sensing neurons (Kress M, 2010). IL-6 sensitizes peripheral nociceptors involved in development of neuropathic pain to mechanical stimuli (Pusztai L et al., 2004). Neuroinflamation and neuroimmunity are activated in a case of chronic pain.

Perioperative pain management can influence the immune response. Epidural analgesia may reduce infectious complications by inhibiting the amount of lymphocytes, reducing the secretion of proinflammatory cytokines as well as improving surgical wound tissue oxygen saturation and promoting healing (Beilin B et al. 2003, Buggy DJ

et al., 2002). Local anesthetics may reduce postoperative inflammatory response in two ways: they block neurotransmission by nerve fibers at the site of tissue damage, weakening neurogenic inflammation of the activation way and reduce post-operative pain due to direct inhibitory effect on inflammation. For continuous epidural or patient controlled epidural analgesia opioids and local anesthetics are commonly used, which allows to reduce the opioid dose while maintaining or even improving the analgesic effectiveness (Hollman MW, Durieux ME, 2000, Shavit Y et al., 2006).

The appropriate choice of anesthesia and postoperative analgesia methods allow the proper management of postoperative pain in patients (Bonnet F, Marret E, 2005) undergoing laparoscopic colorectal surgery, prevention or at least reduction the side effects and reactions to such factors as surgery, long-term pneumoperitoneum, non-physiological position of the patient during surgery, opioids, as well as patient‘s comfort improvement after surgery and long-term hospitalization prevention. New opportunities applied separately do not guarantee more intense post-operative recovery acceleration, but combined with the other elements of perioperative care - laparoscopic technique, anesthesia methods, non-invasive monitoring techniques of cardiac and respiratory functions, used in complex, not only may improve the management of the patient's condition during surgery, but also may facilitate healing after surgery.

2. THE AIM OF THE STUDY

The aim of the study is to compare general endotracheal and combined endotracheal epidural anesthesia impact on organ systems and describe the systems parameters in laparoscopic colorectal surgery.

3. OBJECTIVES

1. Determining the hemodynamic and respiratory parameters trends in patients undergoing laparoscopic colorectal surgery under general and combined anesthesia methods.
2. Comparing perioperative analgesia techniques used in laparoscopic colorectal surgery.
3. Comparing the volume of infusion therapy and measures ensuring hemodynamic stability and frequency of their application during general and combined anesthesia for the patients undergoing laparoscopic colorectal surgery.
4. Determining the impact of anesthesia and postoperative analgesia methods on patients' tracheal extubation time, intestinal motility recovery rate, duration of hospitalization and inflammatory response.

4. SCIENTIFIC NOVELTY

Modern medical and scientific literature analyses the complex methodology, surgical and anesthetic techniques and postoperative care options for customization and enhanced recovery after surgery. Laparoscopic colorectal surgery is not only to provide additional opportunities for the patient to get well soon, but pose challenges and problems associated with operating factors – long term pneumoperitoneum, non-physiological patient's position and other factors on the patient's body systems, and the ability to compensate these operational effects.

Opportunities of different anesthesia instruments to manage and reduce colorectal laparoscopic operating factors on the patient's physiological systems have not been analysed in Lithuania. The scientific literature examines the impact of anesthetics and anesthetic methods on the body stress response and immune system modulation. The results of the research investigating anesthesia effect on inflammatory response are rather contradictory and in the global scientific context there is a necessity of further research in this field. This kind of research has not been performed in Lithuania yet. The

doctoral dissertation analyses the impact of epidural analgesia method on the body stress response, investigating variations of cortisol and interleukin-6 levels.

5. PATIENTS AND METHODS

Upon the permission of the Vilnius Regional Biomedical Research Ethics Committee 2010 05 05 No. 158200-05-181-056LP21, a prospective study was conducted at Vilnius University, Faculty of Medicine, Anesthesiology and Intensive Care Clinic of Anesthesiology, Intensive Care and Pain Management Centre, Vilnius University Hospital Santariskiu Clinics.

5.1. Study population

Having applied inclusion and exclusion criteria the data of 71 (from 78 who signed agreement) patients, who underwent laparoscopic colorectal surgery in Vilnius University Hospital Santariskiu Clinics, were prospectively collected and analysed. The following exclusion criteria were applied: age less than 18, persistent coagulopathy (according APTT, SPA), patient's refusal, conversion of the operation from laparoscopic to open surgery.

Each patient having signed the consent was given a unique patient number in chronological order of enrolment. This patient's number corresponded to the respective questionnaire number and was used to identify the patient throughout the trial. All eligible patients for surgery received the lowest available randomisation number from the randomisation schedule list. The randomisation schedule was generated by an independent statistic expert in advance using SAS PROC PLAN procedure, which automates the random assignment of treatments to randomisation numbers. The randomisation schedule linked sequential numbers to treatment group codes allocated at random with a 1:1 randomisation ratio. The randomisation numbers were blocked. Within each block, the same number of patients was allocated to each of the two treatment groups.

The enrolled patients were randomly divided into two groups: intravenous (IVA) and epidural (EA) analgesia. Analgesia during surgery was allocated according to the

needs. Different analgesia methods were applied to IVA and EA groups: the first group, IVA patients received intravenous opioids (fentanyl, morphine) during the surgery and continuous patient-controlled analgesia (PCA) with morphine sulphate intravenous infusion after the surgery. For the second group−EA patients, analgesia during and after the surgery was guaranteed using epidural method. General anesthesia was given for each patient.

5.2. Anesthesia and surgery technique

The enrolled patients underwent the planned laparoscopic colon resection following the methodology approved by Vilnius University Hospital Santariskiu Clinics (VUL SK) Abdominal Surgery Clinic. Preoperative anesthetic examination, conventional tests before and after the surgery were performed by VUL SK approved methodology. The testing in cortisol and interleukin-6 levels was carried out three times: before induction of anesthesia, immediately after the surgery and 24 hours after the first test. For statistical analysis non-invasive measurements of capture during anesthesia in certain stages of operation were used: 1) 5 minutes after tracheal intubation, 2) 15 minutes after the start of the laparoscopy, 3) after 10 minutes from minilaparotomy, 4) stage of relaparoscopy, 5) at the end of the operation (after closure of the incision). Standard postoperative care was applied after the operation.

All patients, regardless of the group assigned, were given the same premedication with midazolam 2,5 mg half an hour before induction, prevention of nausea and vomiting (8 mg dexamethasone intravenously), non-steroidal anti-inflammatory drugs (NSAIDs) – diclofenac 75 mg, prehidratation with crystalloids 10 ml/kg, general anesthesia induction with intravenous anesthetic (propofol) and intermediate-acting muscle relaxant (atracurium), maintenance of anesthesia by the same inhalation anesthetic (sevoflurane). During the operation, cardiac output measurements were used to prevent the exchange of more than 10% from baseline. Fluid infusion during the surgery maintained with crystalloids and colloids, if necessary to ensure hemodynamic using ephedrine. All patients were intubated by an appropriate size endotracheal tube and the surgery was performed. After the confirmation of the tube position, ventilator

breathing volume and frequency of maintenance in accordance with $EtCO_2$ readings were applied.

Analgesia during the surgery was allocated according to the needs. Different analgesia methods were applied to IVA and EA groups: the first group, IVA patients received opioids (fentanyl, morphine) intravenously during the surgery and continuous patient-controlled analgesia (PCA) with morphine sulphate intravenous infusion after the surgery. For the second group - EA patients, analgesia was guaranteed by epidural method. Thoracic epidural catheter was inserted at Th_{11-12} level before the operation on the very day of surgery, having been assured of the correct position of the catheter (injection of a test dose of lidocaine 1 mg/kg) the local anesthetic bupivacaine from 0.125 to 0.25 % solution 30 ml in total during half an hour and 2 mg (for patients weighing less than 50 kg) or 3 mg (for patients weighing more than 50 kg) of morphine hydrochloride was injected. Further analgesia during the operation was carried out on the need using epidural technique. EA patients post-operative pain relief was provided by using continuous epidural infusion as needed. Epidural infusion solution consisted of 0.25% bupivacaine with 5 mg of morphine hydrochloride in ten millilitres. Both groups received the identical vital signs monitoring, performed the same tests and measurements in the perioperative period.

All operations were performed using the same laparoscopic surgical technique according to a standardized methodology. After the surgery, the patient was transferred to the postoperative ward or the intensive care unit, where he was awakened and extubated.

5.3. Non-invasive respiratory, heart, brain, muscle relaxation measurement methodology

The study applied a non-invasive blood pressure, pulmonary function parameters, and stroke volume, cardiac output and cardiac index determination method, using the equipment that is based on non-invasive operation principles and calculation formulas for further practice to avoid invasive monitoring techniques and to compare different anesthesia methods on heart and lung function parameters variation during laparoscopic colorectal resections. Used equipment:

• Anesthesia machine used during anesthesia (Datex S/5Avance, Excel, FleximaII etc.) monitoring system. Patients' heart rate, blood pressure, respiratory gas composition, entropy, muscle relaxation were recorded by integrated sensors.

• Noninvasive cardiac and respiratory monitoring system (NICO 7300), which calculates stroke volume, cardiac output and cardiac index using the non-invasive respiratory gas analysis-based on modified Fick´s equation. The system, acting on respiratory mechanics mode, provides capnography air data of flow and pressure, and pulse oximetry. The measured and calculated results are presented immediately.

For pain measurement the study used Visual Analogue Scale (VAS) for pain - shown in line of numbers from 1 to 10, arranged from left to right. The numbers increasing to the right of scale correspond to the intensity of the pain: number of 0 means the absence of pain, 10 means unbearable, the most intense pain.

Patient satisfaction is determined by using a similar scale of ten numbers, where 1 corresponds to the most favourable assessment, and 10 to the worst possible patient's condition from the patient point of view. Patients evaluated their condition once, the day after the operation.

Bromage scale was used to monitor the motor block of lower extremities after the surgery. On this scale, motor block intensity is measured by the patient's ability to move his feet.

5.4. Data collection

A retrospective collection of patient demographic information - gender, age, height, weight, BMI, the underlying disease, the patient's condition by the American Association of Anesthesiologists physical status classification, body surface area was made. Preoperative data were collected to characterize the two examined groups of patients- with co-morbidity and other factors that may affect postoperative complications or the operation and anesthesia duration.

Prospectively collected patient´s data were divided as follows:

- The name of the operation performed, duration of anesthesia and operation, requirement for medications during and after the surgery, complications of anesthesia during and after the surgery.
- Patients' hemodynamic condition indicators – during anesthesia and postoperatively: non-invasive measurement of arterial blood pressure (systolic, diastolic, mean), heart rate, sympathomimetic dose, if used, the volume of infusion therapy, colloid content, if used. Data obtained from non-invasive cardiac and respiratory functions monitoring system (NICO 7300) during anesthesia - stroke volume, cardiac index and cardiac output.
- Intra-abdominal pressure during surgery monitored using laparoscopic operating system measurements.
- Respiratory data (obtained from the anesthesia machine and non-invasive cardiac and respiratory functions monitoring system (NICO 7300)) - during anesthesia. Pulse oximetry, tidal volume, ventilation rate, minute volume, oxygen concentration, the maximal pressure in the airways on inspiration process (PIP), minute alveolar volume (Mvalv), dynamic compliance, airways resistance, value of end-expiratory CO_2, an inhaled anesthetic concentration.
- The need of relaxants during the surgery and motor blockade depth during anesthesia – following the display of anesthesia machine and calculated the total demand of relaxants during the operation.
- Entropy method for measurement the depth of anesthesia (obtained from the anesthesia machine) - during anesthesia.
- Post-operative pain and analgesia efficiency. Patient satisfaction and pain in the postoperative period was assessed using visual analogue scale. Patient pain assessment and pain management was performed by acute pain service members, anesthesiologists, anesthesia nurses, surgeons and residents. Post-operative pain management applied to the patient's group assignment, if needed additional pain relief was assigned regardless of the study group. The total amount of postoperative morphine consisted of morphine used the first and second day, additional consumption of morphine and tramadol, converted into morphine, administered the first and second day.

- Leg motor blockade and severity in post-operative period (Bromage scale) assessed if epidural analgesia was used. Evaluated by the primary investigator.
- Intestinal motility: peristalsis - immediately after the surgery, as well as the dynamics after the operation. Intestinal motility assessment by auscultation, repeated periodically, start of liquid food consumption, the time to defecation assessed by the researcher or surgeon or resident physician.
- Excretory system-hourly and daily diuresis- in perioperative period.
- Clinical and biochemical blood tests were carried out routinely in the perioperative period, including C-reactive protein levels on 1-3^{d}, 4th, 6th day after the surgery, as well as cortisol and interleukin-6 levels before anesthesia, immediately after the surgery, and 24 hours after the first test, as a daily rate of concentration change is intrinsic for cortisol.

5.5. Statistical analysis

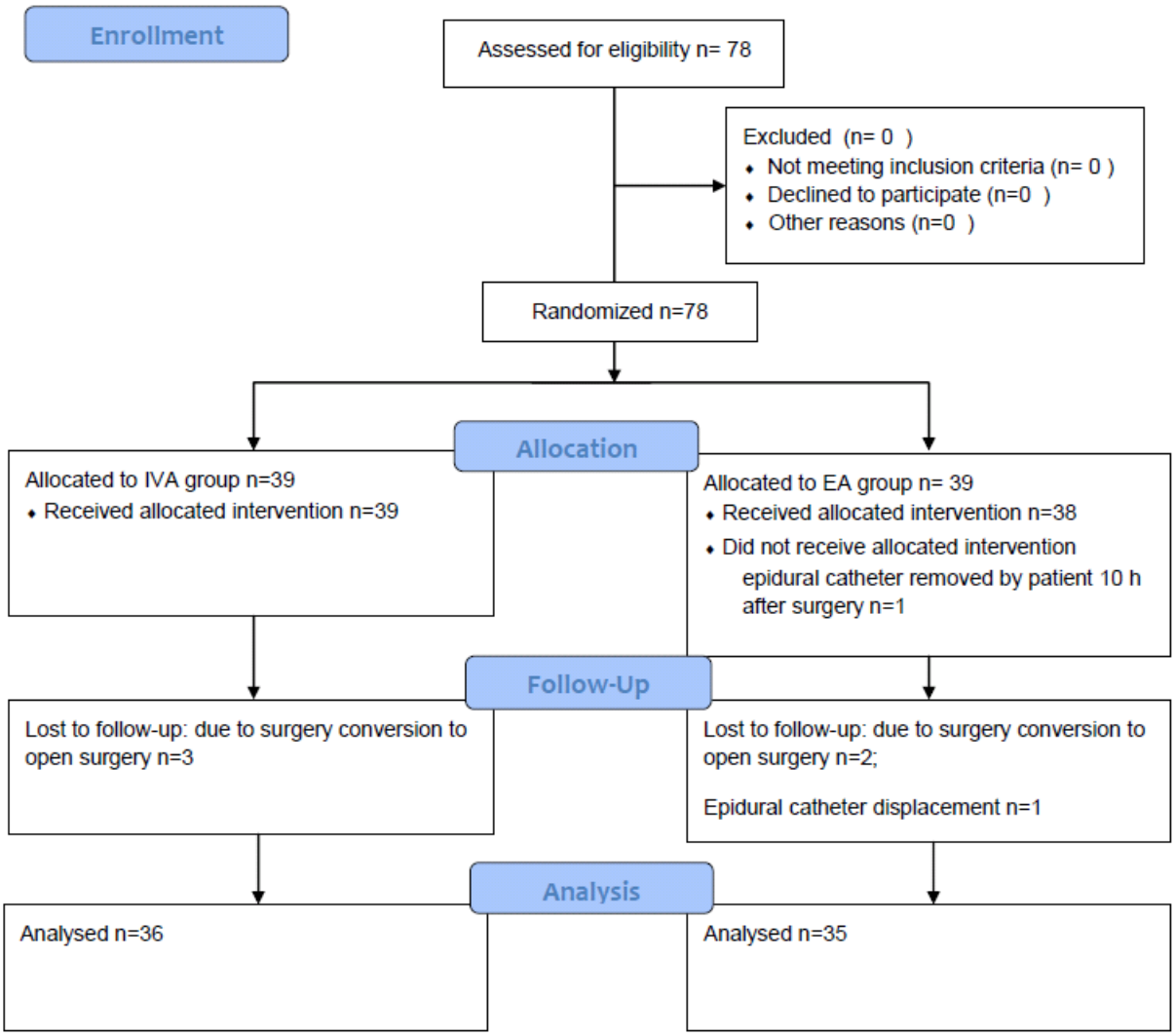
The collected data were accumulated in the Microsoft Excel data base. Statistical analysis was performed using SPSS version 16.0, (SPSS Inc., Chicago, IL, USA). Continuous variables were summarised by using descriptive statistics, i.e. generally displaying number of patients, mean, standard deviation, minimum, median and maximum. Categorical variables were summarised by using frequency counts and percentages. Chi-square or Fisher's exact test were used to compare proportions between two treatment groups. For between-group comparisons of continuous variables, unpaired t-test or Mann–Whitney U test were used as appropriate after checking normality of distribution. Pearson correlation was used to correlate colloids versus ephedrine usage and total post surgery diuresis. All statistical tests were two-sided and a $p \leq 0.05$ value was considered statistically significant.

6. RESULTS AND DISCUSSION

6.1. General characteristics of subjects

78 patients agreed to participate in the study. 71 patient's data was used in the statistical analysis between the randomised groups.

Figure 1. Selected for the survey, followed up and analysed patients' chart



The predominant pathology of the study patients was cancer in various parts of the colon- 74.6 %, tubulovillous adenoma – 8.5%, rectal elongation (dolichocolon) – 7.0%, colonic diverticulosis – 5.6%, other diseases (e.g., adenoma, lipoma) was 4.2%. Comparing the groups according to the predominant pathology a statistically significant difference was not determined, p=0.324.

Overall, the male patients was 23 (32.4%), female - 48 (67.6%). The average age of the patients studied was 64 (mean 63.2 years), the youngest patient was 24 years of age, the oldest – 87. Before the surgery the patient's condition assessment found that 2 or 3 class physical status according to the American Association of Anesthesiologists classification were most common. The total study population and the duration of surgery and anesthesia characteristics by study groups shown in Table 1.

Table 1. General characteristics of the study population

Data		Group IVA (n=36)	Group EA (n=35)	p value
Men [n, (%)]		16(44.4)	7(20.0)	
Women [n, (%)]		20(55.6)	28(80.0)	0.042
Age (years, mean±SD)		62.7±9.4	63.6±14.6	0.757
BMI (kg/m^2, mean±SD)		25.8±3.2	24.3±3.4	0.069
BSA (m^2, mean±SD)		1.82±0.21	1.74±0.17	0.066
ASA [n, (%)]	1	2(5.6)	2(5.7)	0.941
	2	22(61.1)	20(57.1)	
	3	12(33.3)	13(37.1)	
Anesthesia duration (min, mean±SD)		197.9±56.3	217.6±43.4	0.105
Surgery duration (min, mean±SD)		165.8±54.1	173.0±43.8	0.542
Length of hospital stay (days)*		8.3±3.8	9.1±6.4	0.892

* Length of hospital stay – time from day of surgery till discharge from hospital; n – number of patients.

Among comorbid conditions prevailed in cardiovascular diseases, such as primary arterial hypertension was 27.8 % - 10 patients in group IVA, 31.4 % - 11 patients in group EA. Two comorbidities occurred in 19.6% of group IVA *vs.* 14.5% in group EA, such as PAH and ischemic heart disease (8.3% in group IVA *vs.*11.4% in group EA), PAH and type II diabetes (5.6 % in group IVA *vs.* 2.9% in group EA). Comparing the groups according to the comorbid disorders a statistically significant difference was not determined, p=0.44. Upon the surgery type and operating surgeon team the significant difference undetermined, respectively p=0.371 and p=0.237. Accordingly, 61.1 % of group IVA and 60.0 % group EA operations were performed by the same surgical team.

6.2. Post-operative pain assessment and analgesic demand correlation with perioperative pain relief method

It was found, that for group EA the need for analgesics was significantly lower at all stages of assessment, except for the need for additional pain relief for the first postoperative day. Total demand for analgesics is detailed in Table 2 below. The needs for additional analgesics for the first day in both groups were not statistically different.

Table 2. Total requirement of analgesics perioperatively

Data	Group IVA (n=36)	Group EA (n=35)	p value
Total consumption of morphine :	28.8±17.31	11.27±3.62	0.000 *
During surgery (mg)	9.72±1.67	2.94±0.24	0.000*
Postoperatively:	18.56±17.08	8.33±3.58	0.000*
1st day (mg)	9.3±3.3	4.0±1.0	0.000*
2nd day (mg)	2.6±6.9	3.7±1.0	0.000*
Additional (mg)	1.6±5.0	0.1±0.4	0.091
Tramadol (mg, converted into morphine):	5.0±10.82	0.57±2.36	0.038*
Tramadol (mg):			
1st day (mg)	30.6±71.0	5.7±23.6	0.121
2nd day (mg)	19.4±46.7	0.0±0.0	0.012*
NSAID (total amount):	277.1±73.5	175.0±80.2	0.000*
1st day (mg)	154.2±30.8	108.6±38.8	0.000*
2nd day (mg)	134.1±52.2	89.4±42.5	0.001*

Data presented as mean ± SD; NSAID – non steroidal anti-inflammatory drugs.
º The total amount of postoperative morphine consisted of morphine used the first and second day, additional consumption of morphine and tramadol, converted into morphine, administered the first and second day; *$p<0.05$. n – number of patients.

Patients' assessment of pain and satisfaction were significantly better in group EA (Table 3). The pain immediately after the surgery more than 3 according to VAS scale score was assessed by nine (25%) patients in group IVA and two patients (5.7%) of group EA as measured after 24 hours - the 13 patients (36.1%) of group IVA and none of group EA. Additional pain relief in both groups for the first postoperative day was not statistically significant: group IVA in addition to 1.6 ± 5.0 mg (mean ± SD) *vs*. group EA

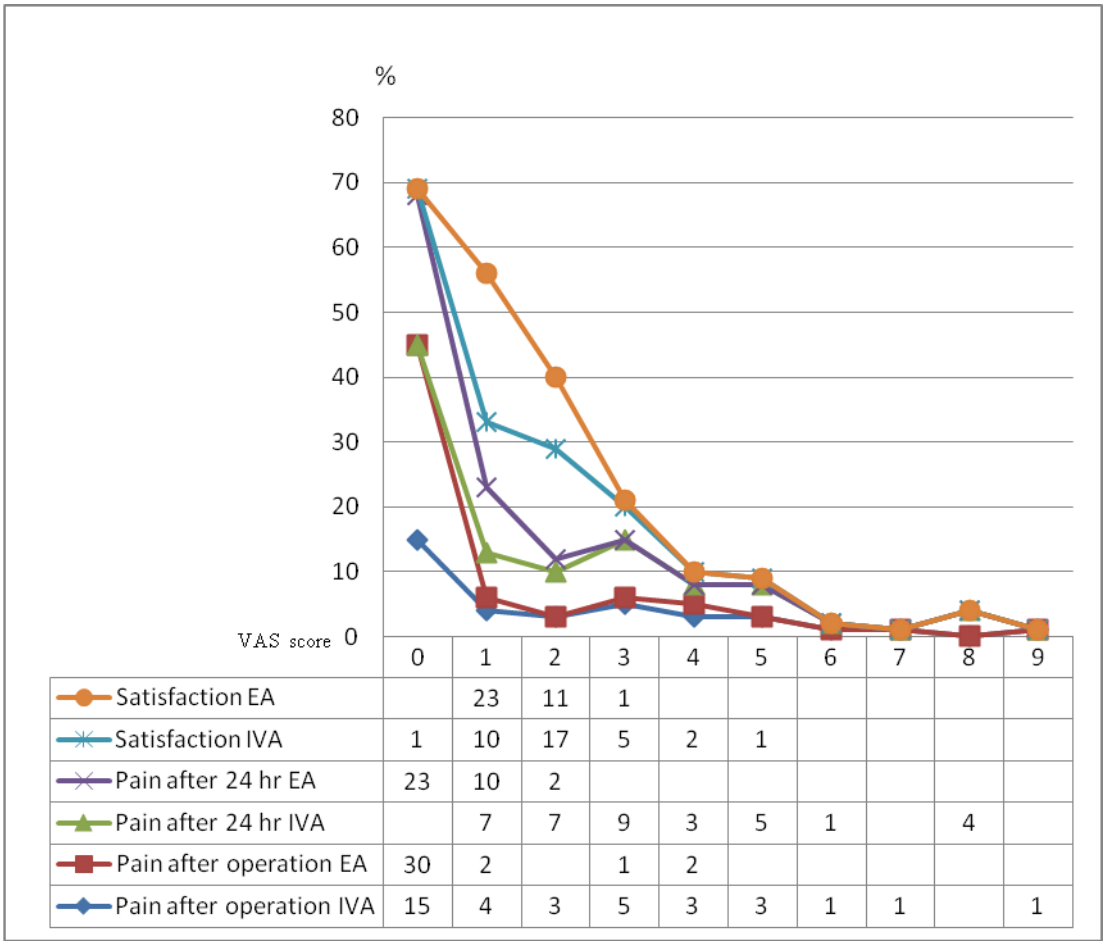
for 0.1 ± 0.4 mg (Table 2). In group EA the pain after the surgery was mostly minimal, 94.2% (32 patients) of patients evaluated by 0 and 1 score. In group IVA postoperative pain score 0 or 1 was assessed by 52.8% (19) of patients (Table 3). Figure 2 shows the pain and satisfaction values distribution in study groups.

Table 3. Patients' pain and satisfaction assessment

Data	Group IVA (n=36)	Group EA (n=35)	p value
Pain (mean±SD)	2.1±2.4	0.4±1.1	0.000
Minimal value	0	0	
Maximal value	9	4	
Pain after 24 h. (mean±SD)	3.4±2.1	0.4±0.6	0.000
Minimal value	1	0	
Maximal value	8	2	
Satisfaction (mean±SD)	2.0±1.0	1.4±0.5	0.002
Minimal value	0	1	
Maximal value	5	3	

n – number of patients.

Figure 2. Pain and satisfaction values distribution of the study groups



	0	1	2	3	4	5	6	7	8	9
Satisfaction EA		23	11	1						
Satisfaction IVA	1	10	17	5	2	1				
Pain after 24 hr EA	23	10	2							
Pain after 24 hr IVA		7	7	9	3	5	1		4	
Pain after operation EA	30	2		1	2					
Pain after operation IVA	15	4	3	5	3	3	1	1		1

6.3. The analysis of hemodynamic variation in selected stages of operation

The difference between groups in first laparoscopy was determined in measurements systolic blood pressure 119 ± 18 mmHg of group IVA *vs.* 102 ± 15 mmHg of group EA, p-0.000 and a diastolic blood pressure 75 ± 11 mmHg vs. 63 ± 9 mmHg, respectively in IVA and EA groups, p-0.000. During the first laparoscopy the mean arterial blood pressure, the absolute and relative changes of MBP between IVA and EA groups also differed significantly. MBP values during the selected stages of the operation, and their absolute and relative changes are shown in Table 4. The heart rate of the selected phases of the operation showed no significant difference.

Table 4. Mean arterial blood pressure variations in selected stages of operation

Data	Group IVA (n=36)	Group EA (n=35)	p value
MBP 1	70.21±15.73	71.34±11.15	0.729
MBP 2	89.24±12.78	75.99±10.17	0.000*
MBP 3	69.49±12.85	66.59±12.22	0.333
MBP 4	85.64±11.89	80.68±12.55	0.092
MBP 5	76.17±11.72	71.20±13.01	0.095
Absolute change			
MBP 2-1	19.03±20.35	4.65±13.18	0.001*
MBP 3-1	-0.72±18.77	-4.75±14.19	0.312
MBP 4-1	15.43±19.22	9.33±13.49	0.128
MBP 5-1	5.95±17.60	-0.14±12.90	0.101
Relative change			
MBP 2/1	33.23±35.84	8.75±21.09	0.001*
MBP 3/1	3.55±33.77	-4.75±20.41	0.216
MBP 4/1	28.04±37.65	15.03±20.55	0.076
MBP 5/1	13.14±29.93	1.33±20.13	0.056

Data are presented as mean±SD; n – number of patients.
MBP - mean arterial blood pressure, mmHg; MBP 2-1= MBP 2- MBP 1;
MBP 2/1=(MBP 2- MBP 1)/ MBP 1×100; *p<0.05

Systolic volume difference during the laparoscopy of group IVA 55.4 ± 14.7 ml *vs.* group EA was 48.2 ± 14.1 ml and cardiac output statistically significant difference at stage minilaparotomy group IVA 3.9 ± 1.3 l/min *vs.* the group EA, 3.3 ± 1.0 l/min at different stages of the operation did not correlate with MBP, SBP and DBP measured

differences. Stroke volume, cardiac output and cardiac index changes in absolute values (Table 5) showed no reliable with MBP changes related differences comparing hemodynamic changes in the IVA and EA groups. Systolic volume and cardiac output trends are depicted in Figures 3 and 4.

Table 5. Comparison of absolute hemodynamic values at selected stages of operation

Data	Group IVA (n=36)	Group EA (n=35)	p value
SV 1	52.3±18.3	51.8±12.7	0.905
SV 2	53.8±18.9	52.3±13.4	0.698
SV 3	60.4±18.4	53.1±15.3	0.074
SV 4	55.4±14.7	48.2±14.1	0.040*
SV 5	61.4±14.5	55.3±17.7	0.115
CO 1	3.4±1.2	3.5±1.0	0.670
CO 2	3.6±1.3	3.5±1.0	0.770
CO 3	3.9±1.3	3.3±1.0	0.026*
CO 4	3.6±1.0	3.3±1.1	0.162
CO 5	3.9±1.1	3.6±1.3	0.187
CI 1	1.8±0.6	2.0±0.6	0.353
CI 2	1.9±0.6	2.0±0.6	0.651
CI 3	2.1±0.6	1.9±0.6	0.120
CI 4	1.9±0.5	1.9±0.7	0.601
CI 5	2.1±0.5	2.0±0.8	0.576

Data are presented as mean±SD; SV – systolic volume, ml;
CO – cardiac output, l/min; CI – cardiac index, l/min×m^2; *p<0,05; n – number of patients.

Figure 3. Systolic volume variation at selected stages of the operation

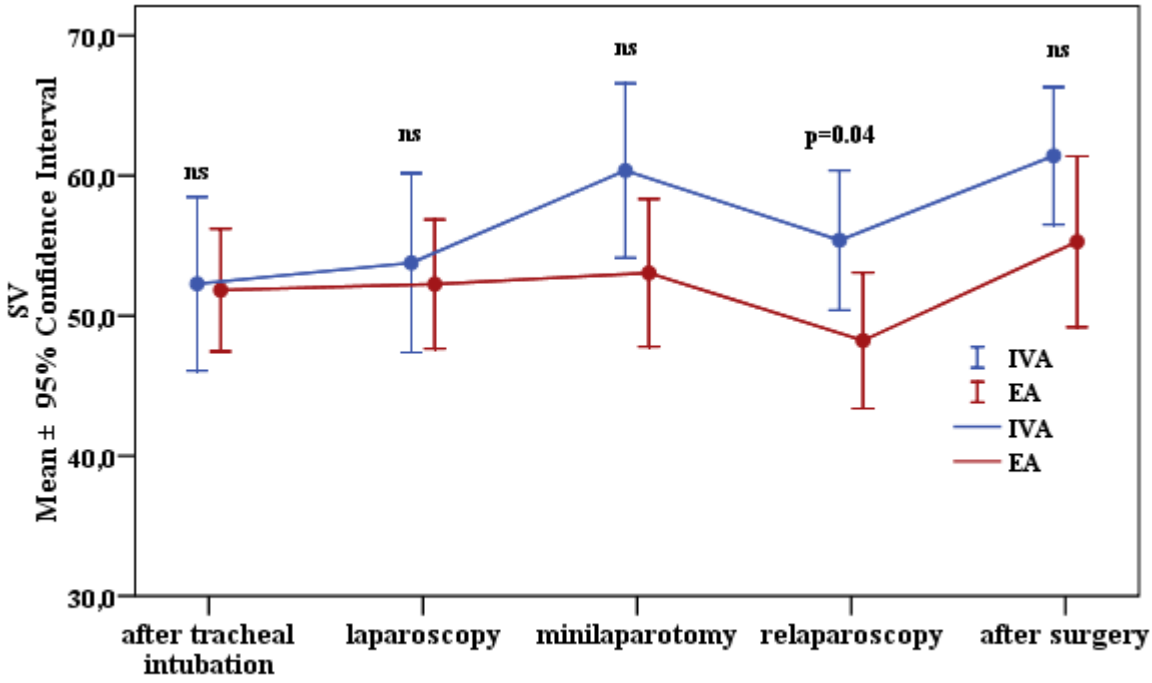
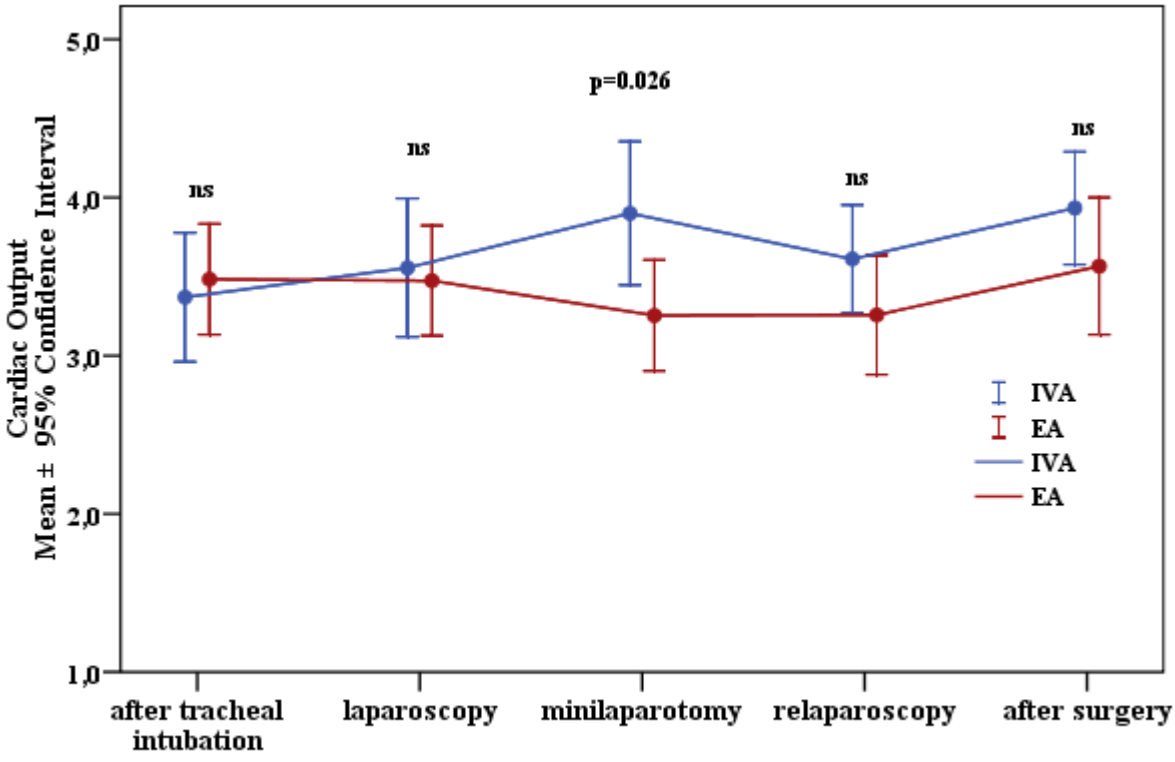


Figure 4. Cardiac output change at selected stages of the operation



In order to determine the effect the epidural blockade has on operating factors induced impact on the cardiovascular system were calculated absolute and relative changes of the parameters − blood pressure, pulse, cardiac output and systolic volume measurements, and changes in cardiac index (Table 6).

Table 6. Comparison of absolute and relative changes of hemodynamic parameters in selected stages between the study groups

Absolute change	Group IVA (n=36)	Group EA (n=35)	p value	Relative change	Group IVA (n=36)	Group EA (n=35)	p value
SV2-1	1.5±15.4	0.4±9.5	0.726	SV2/1	12.2±49.8	2.2±18.9	0.268
SV3-1	8.1±17.7	1.2±10.4	0.051	SV3/1	30.0±68.3	3.8±22.3	0.035*
SV4-1	3.1±14.7	-3.6±10.6	0.032*	SV4/1	19.3±62.6	-5.4±22.0	0.030*
SV5-1	9.1±14.9	3.5±11.5	0.077	SV5/1	32.8±66.0	7.1±23.5	0.033*
CO 2-1	0.19±1.02	-0.01±0.65	0.343	CO 2/1	11.96±36.87	1.40±17.53	0.130
CO 3-1	0.53±1.23	-0.23±0.72	0.002*	CO 3/1	24.29±42.01	-4.46±20.07	0.000*
CO 4-1	0.24±0.91	-0.23±0.76	0.022*	CO 4/1	15.14±37.45	-4.46±23.60	0.011*
CO 5-1	0.56±1.09	0.08±0.85	0.042*	CO 5/1	27.04±43.05	3.42±23.75	0.006*
CI 2-1	0.06±0.56	-0.01±0.39	0.532	CI 2/1	11.13±40.69	1.29±18.62	0.197
CI 3-1	0.25±0.63	-0.13±0.44	0.005*	CI 3/1	23.33±46.00	-4.43±20.46	0.002*
CI 4-1	0.09±0.51	-0.12±0.46	0.066	CI 4/1	13.98±42.66	-4.18±24.03	0.031*
CI 5-1	0.27±0.60	0.05±0.49	0.087	CI 5/1	26.91±50.75	3.49±23.67	0.016*
P2-1	2.42±13.30	-2.31±11.42	0.113	P2/1	6.05±22.20	-2.08±15.94	0.082
P3-1	0.22±10.69	-5.29±11.00	0.036*	P3/1	2.07±17.85	-6.38±16.03	0.040*
P4-1	1.72±10.55	0.37±11.09	0.601	P4/1	4.19±17.79	2.19±17.12	0.631
P5-1	0.58±9.62	-3.60±11.63	0.103	P5/1	1.99±15.56	-3.40±18.14	0.183

Data are presented as mean±SD; n – number of patients.
SV – systolic volume, ml; CO – cardiac output, l/min;
CI– cardiac index, l/min×m^2; P – pulse, beats/min; SV2-1=SV2-SV1,
by analogy CO, CI, P; SV2/1= (SV2-SV1)/SV1×100, by analogy CO, CI, P.

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Generally arterial blood pressure is monitored during anesthesia. Difference in absolute and relative changes between groups IVA and EA were determined only during the first laparoscopy stage (Figure 5 and 6).

Figure 5. Dynamics of average systolic blood pressure of the treatment groups at selected stages of the operation

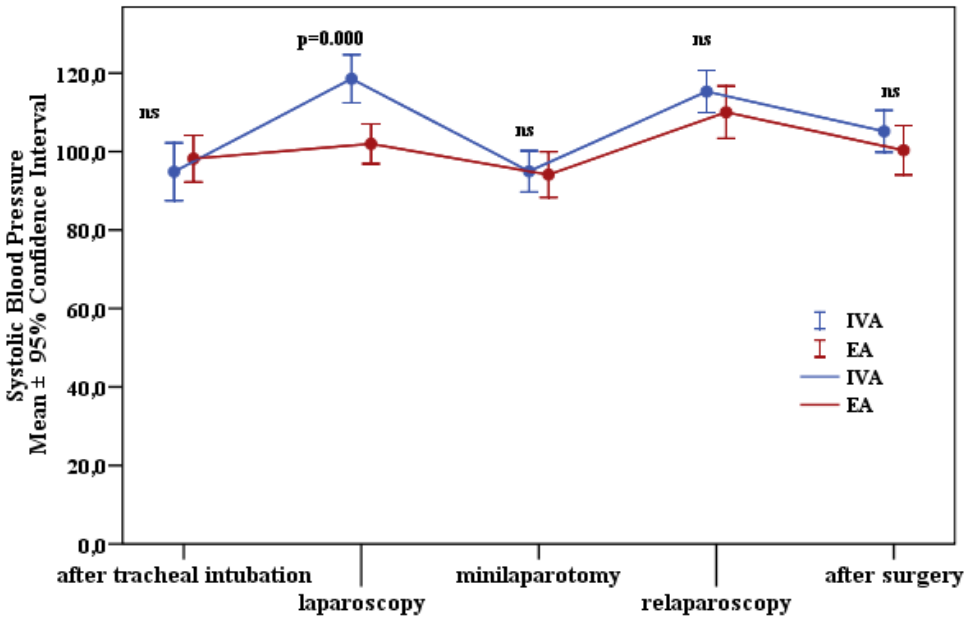
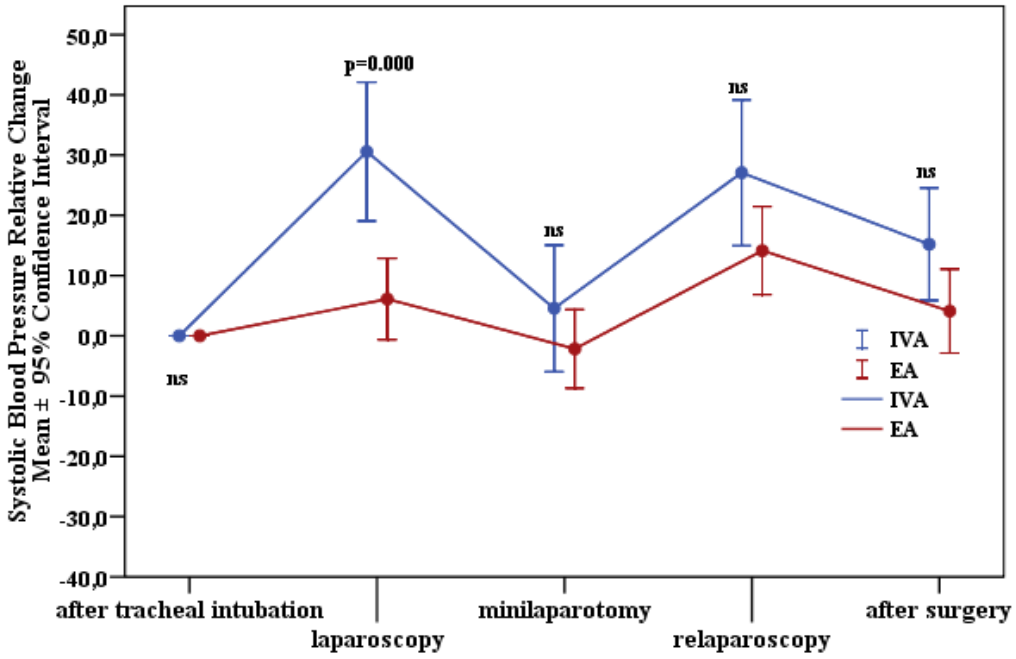


Figure 6. Dynamics of relative changes of systolic blood pressure of the treatment groups at selected stages of the operation



Relative change of cardiac index between the groups was significantly lower in group EA compared with group IVA (Figure 7 and 8).

Figure 7. Average cardiac index variation at selected stages of the operation

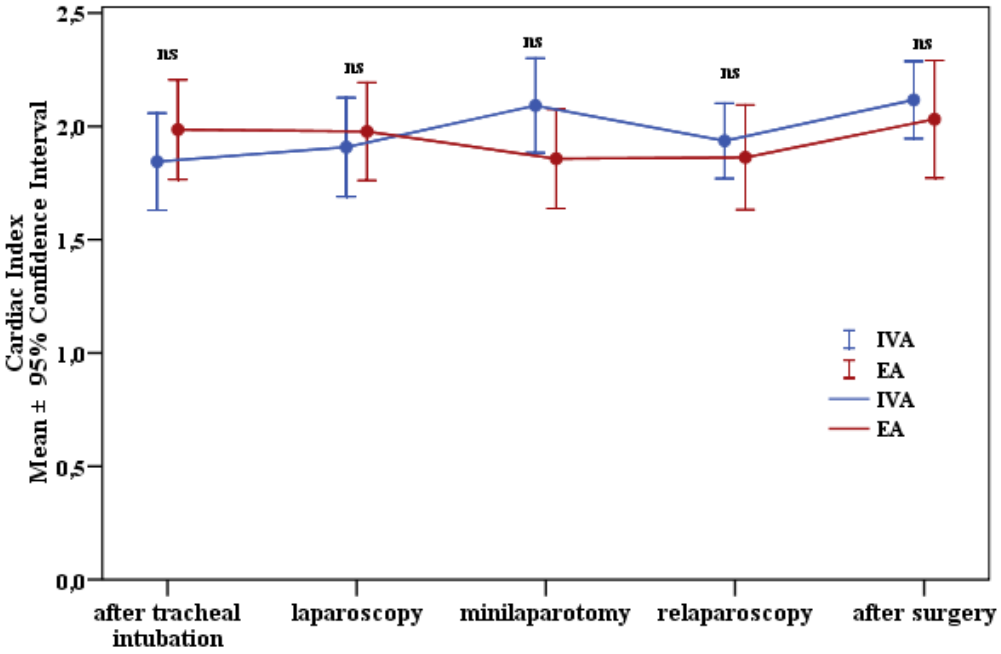
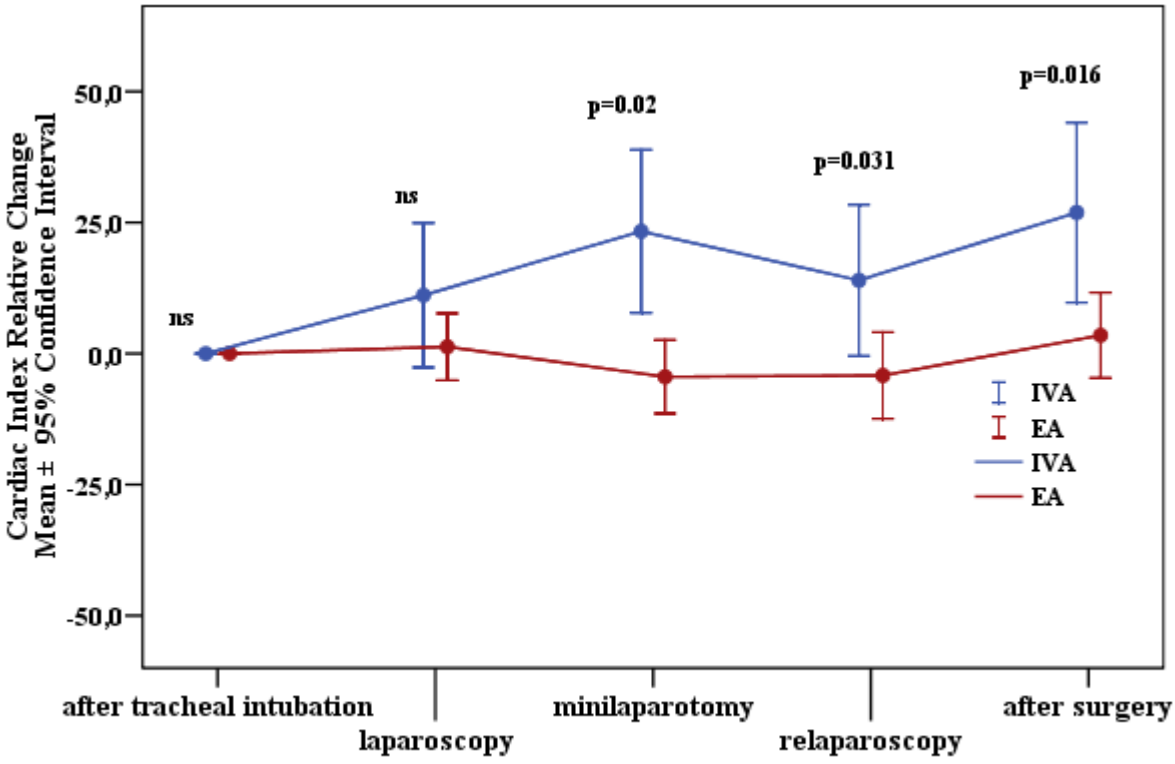


Figure 8. Variation of cardiac index of relative changes



6.4. Crystalloids, colloids, ephedrine, diuresis

Infusion therapy solutions and the quantity, ephedrine need during anesthesia, diuresis in the perioperative period were compared. The first postoperative day crystalloid infusion volume and diuresis in both groups were not statistically significant different. Colloid infusion (500 ml) was used in 15 patients of group IVA (41.6%) and 27 patients in group EA (77.1%). Ephedrine was used for 9 patients (25%) in group IVA and for 19 (54.2%) patients in group EA, the average 11.1 ± 4.2 *vs.* 20.0 ± 13.9 milligrams respectively (mean ± SD). Ephedrine and colloids for group EA patients were used for hemodynamic support statistically significant more, but it did not affect renal function. Diuresis during the surgery and the first postoperative day was not statistically significant different in both groups of patients (Table 7).

Table 7. Infusion therapy volume and diuresis the first postoperative day

Data	Group IVA (n=36)	Group EA (n=35)	p value
Crystalloid volume, ml	2222±591	2457±623	0.116
Colloid volume, ml	194±247	386±213	0.001*
Ephedrine, mg	3±5	11±14	0.003*
Diuresis during operation, ml	370.8±241.5	374.3±247.2	0.991
Daily urine output, ml	1481.9±669.5	1644.3±790.0	0.482

Data are presented as mean±SD; *$p<0.05$; n – number of patients.

6.5. Analysis of intestinal function

Intestinal motility observed immediately after the surgery in 19 patients of group IVA (52.8%) and 34 patients (97.1%) of group EA, the groups differed statistically significant (p-0.000). Within a day, the intestinal motility in both groups of patients was not different: motility in group IVA was observed in 35 of 36 patients (97.2%) and 34 of 35 (97.1%) in group EA, p-0.984. Examining intra-abdominal pressure during laparoscopy episodes of surgery, as a possible factor affecting postoperative intestinal motility, differences between groups were not found (Table 8).

Table 8. Intra-abdominal pressure during two episodes of laparoscopy

Data	Group IVA (n=36)	Group EA (n=35)	p value
Intra-abdominal pressure (first laparoscopy), mmHg	10.75±1.381	10.83±2.007	0.848
Intra-abdominal pressure (second laparoscopy), mmHg	11.06±1.286	10.40±1.786	0.082

Data are presented as mean±SD. n – number of patients.

According to the time before the start of the liquid food intake difference between the groups was found - both groups of patients began to eat at an average the second day after the operation (mean ± SD) group IVA was 2.5 ± 1.1, and group EA 2.3 ± 0.6, (p-0.605). Regarding the analysis of time of first defecation, no significant difference was observed. All patients had defecation the fifth postoperative day, group IVA – 5.2 ± 1.7 (mean ± SD) *vs.* group EA – 4.8 ± 1.8 days, p-0.183.

6.6. Complications

No statistically significant difference between the groups IVA and EA in relations to complications were identified, p-0.380. Complication rate and the number presented in Table 9.

Table 9. Complications rate

Data	Group IVA (n= 36)	Group EA (n= 35)
Without complications	27 (75.0%)	23 (65.7%)
With complications	10 (25.0%)	13(34.3%)

n – number of patients.

In one case reported in group EA III º motor blockade, lasted for 6 hours. One patient of group IVA had longer CMV. Complications related to the bowel anastomotic insufficiency and permeability occurred in three patients (8.3%) of group IVA patients *vs.* two patients (5.7%) of group EA. Three patients, two in group EA and one patient in

group IVA had two different combinations of complications (fever and cardiovascular problem, fever and neuropathy, anastomotic leakage with peritonitis and neuropathy).

6.7. Respiratory function changes

CMV reliably shorter duration after the surgery was in group EA - mean of 15.0 minutes comparing to group IVA – 22.5 minutes, p-0.032. Relaxants consumption in both groups was not statistically significant different (Table 10).

Table 10. Time to extubation and consumption of relaxants

Data	Group IVA (n=36)	Group EA (n=35)	p value
Time to extubation, min (mean±SD)	38.8±90.9	15.3±11.1	0.032*
Amount of relaxants, mg (mean±SD)	54±16	54±19	0.817

*$p<0.05$; n – number of patients.

Reliable carbon dioxide elimination (VCO2) difference between the groups IVA and EA in all stages the operation, except for the first, were determined, but the absolute and relative changes were not statistically significant different (Table 11). Minute ventilation values difference was determined from the minilaparotomy stage. The difference of minute ventilation of absolute and relative change of the values between both groups was not found. Maximum airway pressure values at selected stages of the operation was not statistically significant different, but statistically significant for both absolute and relative changes in laparoscopy time i. e. in group EA, airway pressure increased less – 8.66 ± 3.57 cmH2O (mean ± SD) than in group IVA – 10.69 ± 3.79 cmH2O (mean ± SD) (absolute change in the first laparoscopy), p-0.023, respectively, 7.69 ± 5.01 *vs.* 10.33 ± 4.73 cmH2O (mean ± SD) in the relaparoscopy stage. Similarly, relative changes of maximum airway pressure change rates were found statistically significant different at both laparoscopy stages. The data presented in Figure 9and Table 11.

Figure 9. PIP relative change in the dynamics of the selected stages of the operation

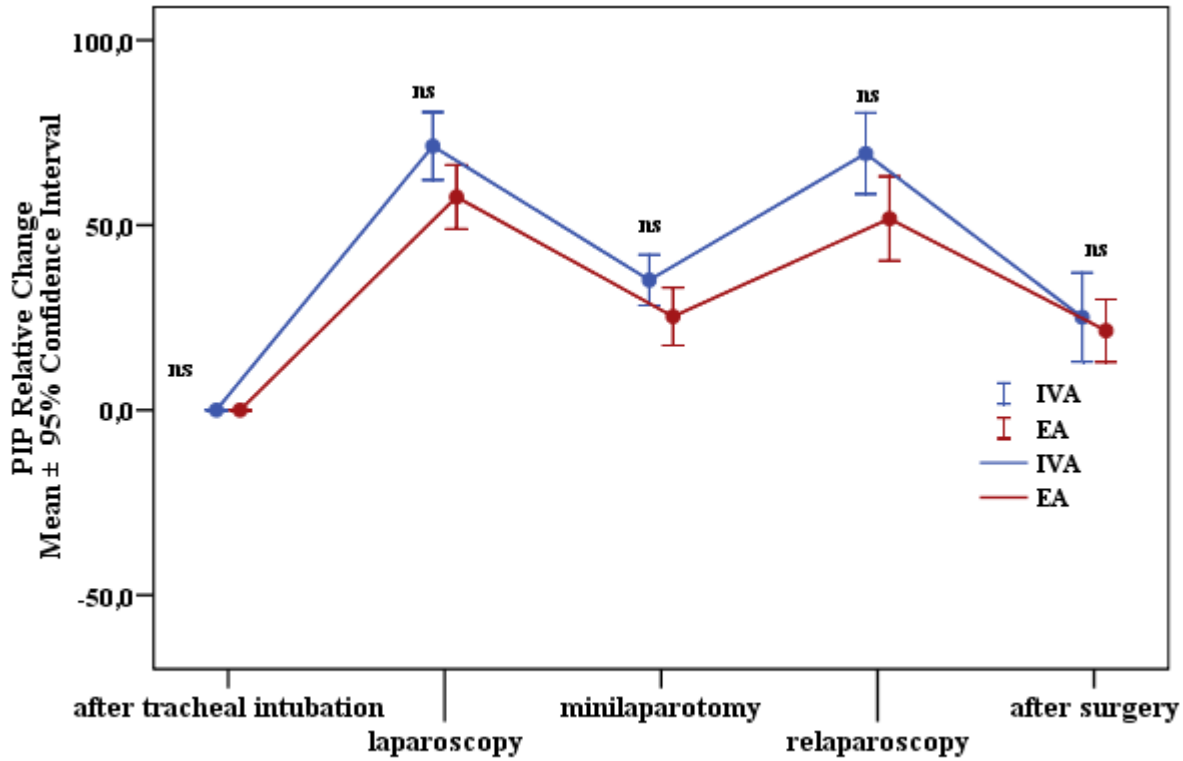


Table 11. Respiratory parameters variations at the selected stages of the operation

Data	Group IVA (n=36)	Group EA (n=35)	p value	Data	Group IVA (n=36)	Group EA (n=35)	p value
VCO_2 1	106.1±23.2	95.6±26.9	0.083	MV 1	6.5±1.5	6.2±1.2	0.308
VCO_2 2	138.2±38.9	113.1±28.5	0.003*	MV 2	7.2±1.6	6.6±1.2	0.071
VCO_2 3	127.6±36.2	109.0±27.5	0.017*	MV 3	7.8±1.4	7.2±1.3	0.049*
VCO_2 4	134.9±33.1	115.5±25.9	0.008*	MV 4	7.7±1.4	7.0±1.2	0.026*
VCO_2 5	133.2±33.5	117.6±26.9	0.034*	MV 5	7.8±1.4	7.2±1.2	0.040*
VCO_2 2-1	32.08±34.62	17.54±27.86	0.056	MV2-1	0.66±1.33	0.38±1.19	0.343
VCO_2 3-1	21.56±27.45	13.40±30.41	0.239	MV3-1	1.29±1.37	0.97±1.27	0.306
VCO_2 4-1	28.78±29.76	19.89±27.98	0.199	MV4-1	1.15±1.32	0.76±1.21	0.203
VCO_2 5-1	27.11±27.44	21.97±26.82	0.428	MV5-1	1.30±1.34	0.98±1.27	0.309
VCO_2 2/1	32.37±34.85	23.90±34.38	0.307	MV 2/1	11.92± 22.25	7.81±20.19	0.418
VCO_2 3/1	20.74±28.34	20.89±42.58	0.986	MV 3/1	22.70± 22.84	17.36±20.62	0.305
VCO_2 4/1	29.91±30.54	27.35±37.13	0.752	MV 4/1	20.30± 22.13	14.13±19.50	0.217
VCO_2 5/1	27.59±30.29	28.72±36.71	0.887	MV 5/1	22.95± 23.13	18.12±20.94	0.360

VCO_2 – carbon dioxide elimination, ml/min; MV – minute ventilation volume, l/min;
$VCO_2$2-1=$VCO_2$2-$VCO_2$1 absolute change of carbon dioxide elimination,
$VCO_2$2/1=($VCO_2$2-$VCO_2$1)/$VCO_2$1×100 – relative change of carbon dioxide elimination; by analogy absolute and relative changes of MV; *p<0,05

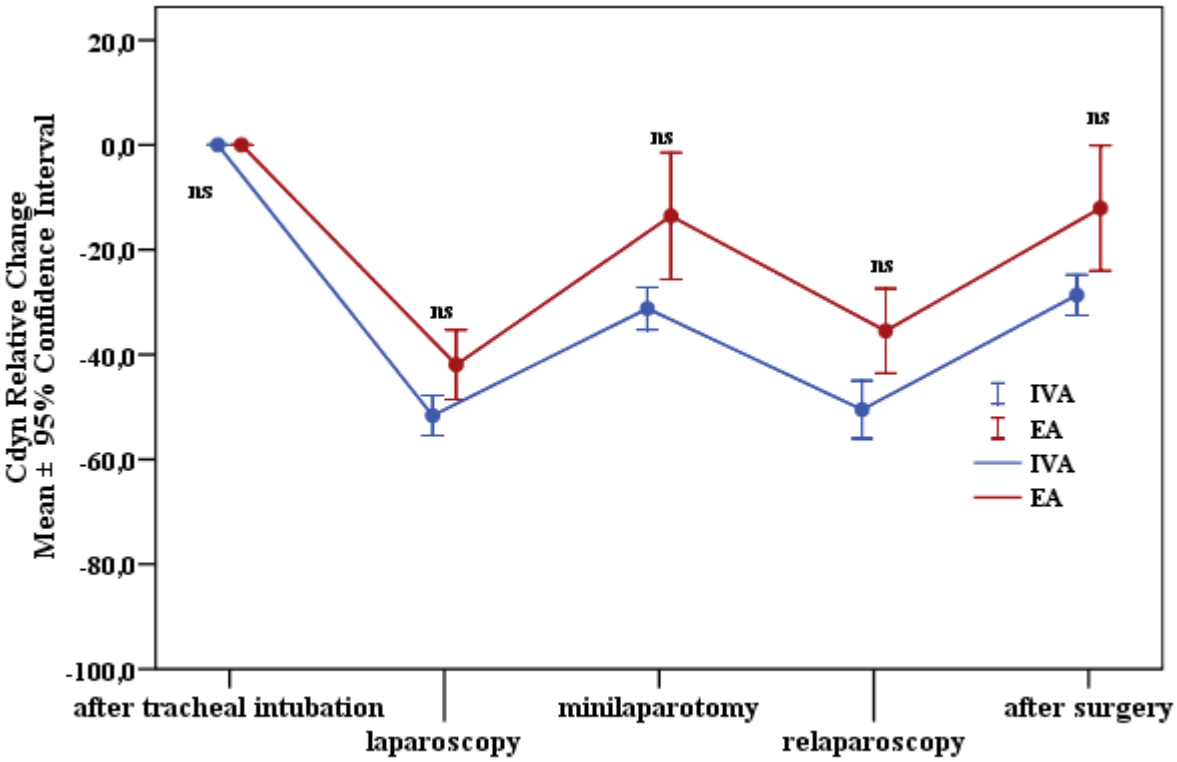
Both groups of patients' dynamic compliance were not statistically significant different, except for the initial measurement, which was significantly lower in EA patients: 57.77 ± 17.07 ml/cmH2O and in group IVA – 67.19 ± 18.39 ml / cmH2O, p-0.029. Examining the absolute and relative changes in the dynamic compliance, group EA experienced a lower airway pressure; because of the dynamic compliance changes were less significant in EA patients than in group IVA (Table 12 and Figure 10).

Table 12. Maximum inspiration pressure and dynamic compliance variation

Data	Group IVA (n=36)	Group EA (n=35)	p	Data	Group IVA (n=36)	Group EA (n=35)	p
PIP 1	15.4±2.9	16.3±4.8	0.328	Cdyn 1	67.19± 18.39	57.77±17.07	0.029*
PIP 2	26.1±5.0	25.0±5.2	0.361	Cdyn2	32.08± 10.16	31.80±7.96	0.896
PIP 3	20.6±3.8	19.9±4.8	0.501	Cdyn3	45.53± 12.64	47.37±17.00	0.605
PIP 4	25.7±5.5	24.0±5.8	0.202	Cdyn4	32.69± 12.56	36.00±14.63	0.310
PIP 5	19.0±5.7	19.0±3.4	1.000	Cdyn5	47.00± 11.51	47.14±10.58	0.957
Absolute change							
PIP2-1	10.69±3.79	8.66±3.57	0.023*	Cdyn 2-1	-35.11± 13.88	-25.97± 13.26	0.006*
PIP3-1	5.19±2.80	3.57±4.29	0.062	Cdyn 3-1	-21.67± 11.65	-10.40± 15.70	0.001*
PIP4-1	10.33±4.73	7.69±5.01	0.025*	Cdyn 4-1	-34.50± 16.03	-21.77± 14.18	0.001*
PIP5-1	3.61±5.41	2.69±4.11	0.420	Cdyn 5-1	-20.19± 11.73	-10.63± 15.19	0.004*
Relative change							
PIP2/1	71.38±27.14	57.60±25.26	0.030*	Cdyn 2/1	-51.64± 11.29	-41.94± 19.29	0.012*
PIP3/1	35.14±20.18	25.30±22.68	0.057	Cdyn 3/1	-31.22± 11.96	-13.55± 35.16	0.006*
PIP4/1	69.34±32.41	51.75±33.16	0.027*	Cdyn 4/1	-50.51± 16.35	-35.49± 23.48	0.003*
PIP5/1	25.08±35.56	21.47±24.55	0.621	Cdyn 5/1	-28.65± 11.45	-12.06± 34.84	0.008*

*p<0.05; PIP – peak inspiration pressure, cmH_2O; Cdyn – dynamic compliance, ml/cmH_2O; PIP2-1=PIP2-PIP1, absolute change of peak inspiration pressure; by analogy Cdyn; PIP2/1= (PIP2-PIP1)/PIP1×100, relative change of peak inspiration pressure; by analogy Cdyn.

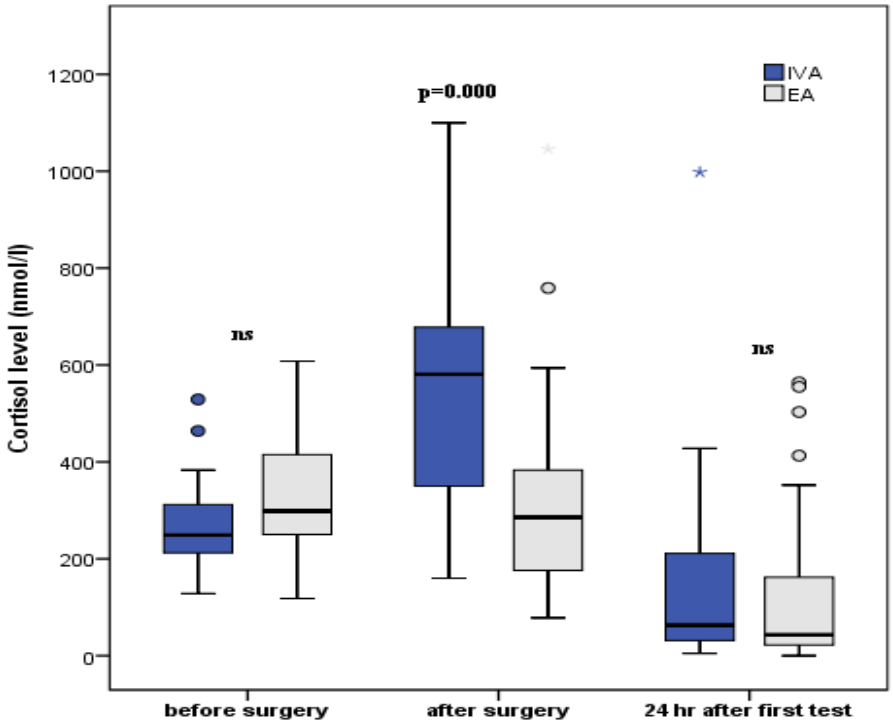
Figure 10. Dynamic compliance the relative change dynamics at the selected stages of the operation



6.8. Cortisol

Statistically significant difference in serum cortisol change in concentration between the groups compared after the surgery and the change before and after the operation were determined (Figure 11). Cortisol level after the surgery was lower in the EA group. In both groups, serum cortisol levels 24 hours after the first test was not statistically significant different (Table 13). (For cortisol applied parametric t test for independent samples).

Figure 11. Cortisol levels in serum changes



Tbale 13. Cortisol levels and changes in serum the first day after the surgery

Data	Group IVA		Group EA		p value
	mean±SD (n)	min; max	mean±SD (n)	min; max	
Cortisol before surgery	265.7±85.3 (35)	128.0; 529.0	311.0±129.9 (35)	10.0; 609.0	0.084
Cortisol after surgery	543.5±227.7 (35)	160.0; 1100.0	330.3±201.9 (35)	78.0; 1046.0	0.000*
Cortisol 24 hr. after first test	146.9±200.5 (34)	5.0; 998.0	127.1±165.2 (35)	0.0; 564.0	0.657
Cortisol change after and before surgey	277.7±216.5 (35)	-69.0; 743.0	18.4±235.9 (35)	-324.0; 631.0	0.000*
Cortisol change 24 hr. after first test and before surgery	-122.2±222.4 (34)	-433.0; 739.0	-184.7±219.9 (35)	-569.0; 385.0	0.244

n – number of patients; min – minimal mean; max – maximal mean; cortisol – nmol/l

6.9. Interleukin-6

In order to check whether the method of analgesia may affect one of the acute phase cytokine levels, IL-6 concentration was measured before the induction of anesthesia, immediately after the surgery and 24 hours after the first test. In groups IVA and EA the results were similar, p>0.05. The results' changes of average values in groups IVA and EA received after the operation compared before the operation, and the test results after 24 hours compared with preoperative values, statistically significant did not differ, p> 0.05. IL-6 numerical values are given in Table 14.

Table 14. Interleukin-6 values and dynamics of changes

Data	Group IVA mean±SD (n)	Group EA mean±SD (n)	p value
Interleukin-6 before the surgery	2.85±1.60 (34)	3.96±4.86 (30)	0.214
Interleukin-6 after the surgery	11.0±9.5 (34)	11.0±7.5 (30)	0.966
Interleukin-6 24 hr. after first test	41.80±169.41 (34)	48.70±180.17 (30)	0.875
Change of interleukin-6 after and before the surgery	8.10±9.60 (34)	7.09±6.63 (30)	0.629
Change of interleukin-6 24 hr. after and before the surgery	38.94±169.38 (34)	44.74±180.64 (30)	0.895

n – number of patients

The correlation between IL-6 values of preoperative and postoperative values (r = 0,283, p = 0,023) and correlation between post-operative and after 24 hours IL-6 values (r = 0,281, p = 0,028) in whole research group were found. Examining the relationship between IL-6 with the possible operational factors showed that IL-6 levels after the surgery increase with the duration of the operation. This is true for both group IVA (r = 0,771, p = 0,000) and group EA (r = 0,528, p = 0,003) and the total group of subjects (r = 0,684, p = 0,000). This correlation remains in group IVA after 24 hours (r = 0,722, p = 0,000), unlike group EA, where such correlations were not noticed.

ANOVA analysis showed that group IVA patients' IL-6 in serum 24 hours after the first test significantly depends on the development of complications (p = 0,036). In group EA, such dependencies were not identified.

6.10. C-reactive protein of changes analysis

C-reactive protein level was studied and compared the first-third day after the surgery, and after four and six days. Average of the first three days of group IVA were 40.68 ± 26.87 (mean ± SD), group EA – 39.0 ± 16.1, p-0.742. Also, the average CRP values did not differ between the groups after 4 and 6 days - p respectively, 0.347 and 0.411. The analysis of whole research group found that 21 (29.6%) patients of 71 had complications and various degrees of disorder. These analysis revealed that the three-day average concentration of CRP in patients without complications was 41.10 ± 25.91 (mean ± SD), and with a history of complications - 79.74 ± 78.68 mg/l, p-0.044. It is also a statistically significant difference in mean values obtained for CRP at 4 and 6 days (Table 15)

Table 15. The study group analysis of the relationship between CRP and complications

Data	Without complications mean±SD (n=50)	With complications mean±SD(n=21)	p value
CRP mean value of 3 days, mg/l	41.10±25.91 (45)	79.74±78.68 (19)	0.044*
CRP 4 days after the surgery, mg/l	34.9±22.8 (40)	102.5±78.9 (18)	0.000*
CRP 6 days after the surgery, mg/l	16.6±10.9 (28)	86.2±100.5 (13)	0.000*

n – number of patients; *p<0.05

Using epidural analgesia also provides a reliable difference in CRP concentration with the presence of complications within groups IVA and EA (Table 16).

Table 16. Bonferroni comparison of CRP levels in groups IVA and EA

Data	Groups of comparison	Mean difference	Std. Error	95% Confidence Interval		p value
				Lower Bound	Upper Bound	
CRP, mean of three days	IVA-B *vs*. EA-B	-.85830	12.97345	-36.2570	34.5404	1.000
	IVA-K *vs*. EA-K	76.03611*	19.98850	21.4965	130.5758	0.002*
	IVA-B *vs*. IVA-K	-79.07850*	17.10466	-125.7495	-32.4075	0.000*
	EA-B *vs*. EA-K	-2.18409	16.59160	-47.4551	43.0870	1.000
	IVA-K *vs*. EA-B	78.22020*	17.21365	31.2519	125.1885	0.000*
CRP 4 days after surgery	IVA-B *vs*. EA-B	-11.3950	14.2750	-50.493	27.703	1.000
	IV-K *vs*. EA-K	57.4111	21.2799	-.873	115.696	0.056
	IVA-B *vs*. IVA-K	-102.0211*	18.1192	-151.649	-52.394	0.000*
	EA-B *vs*. EA-K	-33.2150	18.1192	-82.842	16.412	0.434
	IVA-K *vs*. EA-B	90.6261*	18.1192	40.999	140.254	0.000*
CRP 4 days after surgery	IVA-B *vs*. EA-B	-2.9779	18.7733	-55.310	49.355	1.000
	IVA-K *vs*. EA-K	-21.3452	27.5630	-98.180	55.489	1.000
	IVA-B *vs*. IVA-K	-78.7560*	23.2259	-143.501	-14.011	0.010*
	EA-B *vs*. EA-K	-97.1233*	23.9313	-163.834	-30.412	0.001*
	IVA-K *vs*. EA-B	75.7781*	22.6775	12.562	138.994	0.011*

IVA-B – part of group IVA without complications; IVA-K – part of group IVA with complications; EA-B – part of group EA without complications; EA-K – part of group EA with complications; n – number of patients; *$p<0.05$

7. DISCUSSION

Patients after the surgery feel average and stronger than average pain and the choice of perioperative pain management method remains relevant after laparoscopic colorectal surgery. A.J. Senagore et al. (2003) study demonstrated that better post-operative analgesia can be achieved through the combined epidural and general endotracheal anesthesia. Our study also shows that EA patient's analgesic requirement was significantly lower in all stages of the evaluation. The amount of consumed morphine during surgery was more than three times higher in group IVA than in EA group, in the postoperative period – twice more. Non-steroidal anti-inflammatory drug intake also was statistically significant different. As in G. P. Joshi, F. Bonnet and H. Kehlet (2013) survey, we found that although the level of pain in intravenous analgesia patients' group was higher than in the epidural group, in all cases it did not exceed 4 points out of 10. Our study reveals a reliable assessment of patients' pain difference between the groups. The pain immediately after the surgery was more than 3 points in accordance with VAS scale score of 25% IVA group *vs.* 5.7% EA group patients, and

after 24 hours - 36.1% IVA group *vs.* none of EA group. Satisfaction using a similar 10-point scale was also better evaluated of EA group subjects. Peristalsis was detected immediately after the operation in 52.8% of our patients in IVA group *vs.* 97.1% of patients in EA group. The study of intestinal motility after 24 hours showed no difference between the groups: intestinal peristalsis was found for 97.2% of group IVA, and 97.1% in group EA patients.

Examining intra-abdominal pressure during laparoscopy episodes of surgery, as a possible factor affecting postoperative intestinal motility, differences between groups were not found. In both groups, the intraabdominal pressure was at an average 10-11 mmHg and did not differ significant between the groups in both laparoscopic stages. The data obtained in this study are close to U. Zingg et al. (2009) results: epidural analgesia in laparoscopic colorectal surgery reduces the need for opioids and speeds up bowel movement for recovery in respect of motility, food tolerance and defecation. Regarding the time of the start liquid food consumption our study did not find out the difference between the groups, as the patients of both groups started liquid food eating at an average on the second day after the operation. Significant difference was not received regarding the time of the first defecation. All patients had the first defecation on the fifth day after the surgery.

The survey did not show statistically significant difference between the IVA and EA groups according to the complications rate.

According to the findings of this study, CMV time to extubation for EA patients was shorter by more than two-fold compared with group IVA. This correlates with other authors on published data (Zafar N et al., 2010, Senagore AJ et al., 2003, Canet J, Mazo V, 2010). This study showed that the dynamic compliance statistically significant between the IVA and EA groups did not differ with the exception of the initial measurement, which was significantly lower in group EA. Examining the absolute and relative changes in the dynamic compliance group EA experienced a lower maximum pressure in the airways, resulting in this group of patients the dynamic compliance changes were lower than in group IVA. Other conditions of the study were standardized for both groups; intra-abdominal pressure did not differ significant. Patient positioning– Trendelenburg with the position on the side according the surgery methodology, time and duration of surgery in groups IVA and EA did not differ significant. Although a

minute ventilation values difference was determined from the minilaparotomy stage, in both groups pulmonary ventilation absolute and relative changes in the values the difference was not received. Maximum pressure in the airways at selected stages of surgery did not differ, a statistically significant difference for both the absolute and relative changes between groups IVA and EA were determined. Similarly, different relative maximum airway pressure changes for both laparoscopy stages were obtained; maximum pressure changes in group EA were lower than those in group IVA. Laparoscopic colon surgery diaphragmatic movements limited by pneumoperitoneum increased intra-abdominal pressure and the Trendelenburg position of the patient.

One of the main disadvantages of non-invasive cardiac and respiratory monitoring system based on modified Fick rebreathing method, is that there is a need of patients' help, in case the survey is carried out the patient being conscious (Širvinskas E et al., 2005). In our study all parameters measured only on CMV conditions.

Hemodynamic fluctuations during laparoscopy primarily caused due pneumoperitoneum increased intra-abdominal pressure. During the first laparoscopy the mean arterial blood pressure in IVA and EA groups was significant different, as well as SBP and DBP. In this phase of the operation, both the absolute and relative changes in MBP were significant different. Heart rate and both absolute and relative changes between the groups, at the minilaparotomy stage, did not coincide with changes in blood pressure. Stroke volume, cardiac output and cardiac index showed no change in absolute values reliable with MBP changes related differences comparing IVA and EA groups in hemodynamic changes. This study showed heart rate absolute and relative significant difference between the study groups only at minilaparotomy stage. Absolute HR values in groups IVA and EA did not differ. Examining cardiac output, cardiac index, and heart stroke volume variation, the reliable of the three parameters of relative change between groups, not only in minilaparotomy, but also at other operations stages - relaparoscopy and closing, which did not correlate with the relative change in heart rate was found. Therefore it must be concluded that such changes in relative differences may occur due to general anesthesia and epidural impact on effectively blocking the sympathetic nervous system response to long-term pneumoperitoneum and other operational factors. This assumption is supported by other research studies (Shin et al., 2013, Rist M et al., 2001).

Having compared the need of infusion therapy solutions, ephedrine during anesthesia, diuresis in the perioperative period, we found that in both patients' groups crystalloid infusion volume and diuresis on the first postoperative day was not statistically significant different. Ephedrine and colloid in EA group to maintain hemodynamic was required statistically significant more, but it did not affect renal function, in both groups diuresis during surgery and the first postoperative day was not statistically significant different.

This study showed that epidural analgesia patients' cortisol concentration in the blood serum after the surgery was significantly lower than in the general anesthesia group, i. e. EA patients had a lower stress response than IVA group, better postoperative pain control and patient assessment was more favourable. Inflammatory response in the literature on laparoscopic colorectal resections is not widely studied, indicating the need for further exploration of interleukins concentration variations.

Published research states that the amount of pro-inflammatory interleukins in the perioperative period may be affected by the magnitude of surgical trauma and chosen anesthesia method (Hu JK et al., 2003, Moselli NM et al., 2011, Menges P et al., 2012). Some investigators refer to the amount of interleukins and pain (Watkins LR et al., 1995, Watkins LR et al., 1999, Kuo CP et al., 2006), epidural analgesia and a lower inflammatory response correlation (Moselli NM et al., 2011, Menges P et al., 2012, Kuo CP et al., 2006, Ahlers O et al., 2008, Beilin B et al., 2003, Hong JY, Lim KT, 2008), a lower number of complications for perioperative analgesia using epidural approach (Moselli NM ir kt., 2011). Our records did not show any correlation between pain assessment and interleukin-6 concentrations in serum, epidural analgesia and IL-6 concentration postoperative change. We found the operation and IL-6 concentration correlation after the surgery regardless of the method used in analgesia, suggesting the existence of relationship between IL-6 concentration and the operating trauma. The number of complications according to the applied perioperative pain management methods did not differ. ANOVA analysis for IVA patients found a correlation between interleukin-6 levels in serum after 24 hours from the first test and the development of complications.

For the elective colorectal operations, CRP can be useful in the control of infectious complications (MacKay GJ, 2011). Our study revealed no reliable serum CRP concentration difference between group EA and IVA neither in the first three days nor after 4 or 6 days after the surgery. Correlations were linked to CRP concentration and the occurrence of complications of the study population, in group IVA as well as within the first three days (the average is taken) as after 4 and 6 days. However, in group EA, the correlation between complications and CRP levels was found only after 6 days after the surgery. G. J. MacKay et al. (2011) study indicates complications in regard to safe CRP levels - less than 145 mg / ml on the fourth day after the operation, safe dose of 140 mg / ml indicates T. Welsch and associates (2007), but both of these studies carried out by open surgery. Our analysis of CRP of 102.5 ± 78.9 mg /l after 4 days showed complications regardless of the method used for analgesia. Some authors argue that laparoscopic surgery techniques caused inflammatory response, which, according to CRP and IL-6 values are not different from open techniques. This is explained by surgical disturbance of bowel integrity, which is common to both operation procedures (Tang CL et al., 2001, Fukushima R et al., 1996, Dunker MS et al., 2003).

8. CONCLUSIONS

1. The patients' using combined endotracheal epidural anesthesia hemodynamic fluctuations were less significant.

The change of dynamic compliance was lower according to the interaction controlled mechanical ventilation with intraabdominal pressure using combined endotracheal epidural anesthesia.

2. Analgesia and patient satisfaction using epidural analgesia method for perioperative pain management was better.

3. The volume of crystalloid infusion therapy was not inconsistent between the different methods of analgesia groups. The need of colloids and ephedrine for hemodynamic stabilization was more frequent using the epidural analgesia method.

4. 4.1. Tracheal extubation time was significantly shorter in combined endotracheal epidural anesthesia group.

4.2. Recovery of intestinal motility in group EA was significant and much prior than in group IVA.

4.3. The use of epidural analgesia in laparoscopic colorectal surgery caused less stress response – less cortisol levels increase, and it does not proved the increase in number of complications. Using the combined endotracheal epidural anesthesia lowers the cortisol level rise immediately after the surgery. Our data show that IL-6 concentration correlated with the duration of the surgery, rather than the method of analgesia. CRP levels did not demonstrate any significant changes in the method of analgesia effects.

4.4. Unproven influence of method of analgesia on patients' length of hospital stay, liquid food intake and first defecation time after the surgery.

9. PRACTICAL RECOMMENDATIONS

1. Combined endotracheal epidural anesthesia is appropriate in laparoscopic colorectal operations as it helps to reduce the body's response to stress, provides proper management of post-operative pain and gives patients′ better satisfaction.
2. Combined endotracheal epidural anesthesia is appropriate using an enhanced recovery protocol in colorectal surgery as it does not extend the patients post-operative length of stay in hospital, and does not increase the number of complications.

10. LIST OF PUBLICATIONS AND PRESENTATIONS

Publications:

1. Gasiūnaitė D., Šipylaitė J., Kontrimavičiūtė E. Anesthesia and analgesia for laparoscopic colorectal surgery. Theory and Practice in Medicine, 2012: 18(1): 75-9.
2. Gasiūnaitė D., Šipylaitė J., Kontrimavičiūtė E., Poškus E. Impact of anesthesia method on cortisol and interleukin-6 concentration changes during and after laparoscopic colorectal surgery. Acta Medica Lituanica. 2012: 19(3): 244-250.

Oral presentations:

1. „Anesthesia for laparoscopic colorectal surgery“, 5th International Baltic Congress of Anesthesiology and Intensive Care (2010, 21-23th October, Tartu, Estonia).

Abstract of the presentation „Anesthesia for Laparoscopic surgery“, Gasiūnaitė D., Šipylaitė J. published in congress papers.

2. „Impact of anaesthesia method on hemodynamic changes during laparoscopic colorectal surgery“, 31th Congress Skandinavian Society of Anaesthesiology and Intensive care Medicine SSAI 2011 (2011 15-17th June, Bergen, Norway).

Abstract of the presentation “Impact of anaesthesia method on hemodynamic changes during laparoscopic colorectal surgery”, D.Gasiūnaitė, J. Šipylaitė, E.Kontrimavičiūtė, published in congress papers.

3. “Implication of anesthesia practice on immunological response to surgery”, 6’th International Baltic Congress of Anesthesiology and Intensive Care (2012 m. 18 – 20th October, Vilnius, Lithuania)

Poster presentations:

1. Gasiūnaitė D., Šipylaitė J. “Epidural morphine and bowel motility restoration in laparoscopic colorectal surgery” 6’th International Baltic Congress of Anesthesiology and Intensive Care (2012 18 – 20th October, Vilnius, Lithuania). Abstract of the presentation published in congress papers.

11. CURRICULUM VITAE

Diana Gasiūnaitė was born in Vilnius, Lithuania, on November 2, 1970.

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Education:

1988 graduated from Vilnius Secondary School No. 41.

1988 - 1995 studies at Vilnius University Medical Faculty.

1995-1996 residential studies at Kupiškis Central Hospital

1996-1999 residential studies in Anesthesia and Intensive Care at the Vilnius University, Faculty of Medicine

2009 - 2013 Doctoral (Ph. D.) studies in Vilnius University Medical faculty.

Professional Experience:

1999 – till present Vilnius University Hospital Santariškių klinikos, Centre of Anesthesiology, Intensive Therapy and Pain Treatment, Ist Department of Anesthesiology and Intensive Care, anesthesiologist.

1999-2004 Hospital St. Jokubas, Vilnius, Department of Anesthesia and Intensive Care, Anesthesiologist and intensive care doctor.

2002-2003 Vilnius University Hospital Antakalnio, Intensive care unit, Intensive care doctor.

2010-till present Vilnius Univrsity, Clinic of Anaesthesiology and Intensive Care, Assistant.

Membership:

European Association of Anesthesiologists (member)

Lithuanian Society of Anesthesiology and Intensive Care (member)

Lithuanian Society of Parenteral and Enteral Nutrition (member)

Languages:

Lithuanian mother tongue

Russian excellent

English excellent

SUMMARY IN LITHUANIAN

SANTRAUKA LIETUVIŲ KALBA

1. ĮVADAS

Šiuolaikinėje medicinos praktikoje susiduriama su pacientų greitos pooperacinės reabilitacijos – spartesnio sveikimo (angl. *enhanced recovery*) poreikiu. Šia linkme mokslinėje literatūroje nagrinėjamos metodikų bei kompleksinių priemonių taikymo perspektyvos bei galimybės, tampa aktualus įprastų anesteziologinių metodikų pritaikymas laparoskopinei kolorektalinei chirurgijai bei naujų galimybių paieška, kad pacientai po operacijos greičiau grįžtų prie įprastos veiklos, kartu būtų užtikrintas geresnis paciento pasitenkinimas. Laparoskopinė chirurgija siejama su mažesniu operaciniu pjūviu ir trumpesniu pooperaciniu diskomfortu bei skausmu operacijos vietoje, tačiau pooperacinio skausmo valdymas išlieka aktuali problema.

Laparoskopinės storosios žarnos rezekcinės operacijos, net ir būdamos minimaliai invazinės dėl laparoskopinės operacijos technikos, sužadina stresinį organizmo atsaką bei uždegimo mediatorių išskyrimą, kuris nustatomas toks pat kaip atliekant atvirąsias operacijas. Perioperacinis stresas gali slopinti tinkamą adaptacinį imuninės sistemos atsaką. Dėl pneumoperitoneumo laparoskopinių operacijų metu padidėja vazopresino ir katecholaminų koncentracija. Hiperkapnija ir pneumoperitoneumas stimuliuoja simpatinę nervų sistemą ir katecholaminų atsipalaidavimą. Chirurginio streso indukuotas hormonų – katecholaminų, AKTH, kortizolio atsipalaidavimas per autonominę nervų sistemą ir PHA sistemą dalyvauja slopinant imunines organizmo funkcijas (Vallejo R irk t., 2003, Kelbel I, Weiss M, 2001). Uždegimą skatinantys citokinai – interleukinas-1 (IL-1), interleukinas-6 (IL-6) ir navikų nekrozės faktorius α (TNF-α), išskiriami monocitų ir makrofagų bei limfocitai, aktyvinti chirurginio streso, gali stimuliuoti PHA sistemą, o neuroendokrininė sistema kartu su citokinais, tiek uždegimą skatinančiais, tiek slopinančiais, sinergiškai papildo perioperacinės imuninės sistemos slopinimą. IL-6 ne tik kontroliuoja imuninių ląstelių sąveiką, bet ir turi įtakos skausmui ir padidėjusiam jautrumui, susijusiems su uždegimu, neuropatija arba vėžiu, tiesiogiai reguliuodamas skausmą priimančių neuronų kiekį (Kress M, 2010). IL-6 įjautrina periferinius nociceptorius mechaniniams dirgikliams (Pusztai L et al., 2004) dalyvauja išsivystant

neuropatiniam skausmui. Lėtinio skausmo atveju aktyvinamas neuroužd egimas ir neuroimunitetas.

Perioperacinis skausmo valdymas gali daryti įtaką imuniniam atsakui. Epiduralinė analgezija gali sumažinti infekcinių komplikacijų kiekį slopindama limfocitus, sumažindama uždegimą skatinančių citokinų sekreciją bei pagerindama chirurginės žaizdos audinių įsotinimą deguonimi bei skatindama gijimą (Beilin B ir kt., 2003, Buggy DJ ir kt., 2002). Vietiniai anestetikai pooperacinį uždegimo atsaką gali sumažinti dviem būdais: jie blokuoja impulso perdavimą nervinėmis skaidulomis audinių pažeidimo vietoje tuo silpnindami neurogeninį uždegimo aktyvavimo kelią bei dėl tiesioginio uždegimą slopinančio poveikio sumažina pooperacinį skausmą. Pastovaus režimo epiduralinei arba paciento kontroliuojamai epiduralinei analgezijai dažniausiai vartojamas opioido ir vietinio anestetiko mišinys, kuris leidžia sumažinti opioido dozę, išlaikant ar net pagerinant analgezinį efektyvumą (Hollman MW, Durieux ME, 2000, Shavit Y ir kt., 2006).

Tinkamas anestezijos būdo ir pooperacinės analgezijos taktikos pasirinkimas leidžia tinkamai valdyti pooperacinį skausmą pacientams (Bonnet F, Marret E, 2005), kuriems atliekamos laparoskopinės storosios žarnos rezekcinės operacijos, išvengti ar bent jau sumažinti nepageidaujamą poveikį ir reakcijas, sukeliamas tokių operacinių veiksnių, kaip chirurginė intervencija, opioidų vartojimas, ilgalaikis pneumoperitoneumas, nefiziologinė paciento padėtis operacijos metu, taip pat pagerinti paciento komfortą po operacijos ir išvengti ilgalaikio gydymo ligoninėje. Naujos galimybės pavieniui negarantuoja ryškesnio pooperacinio sveikimo pagreitėjimo, bet derinamos su kitais perioperacinės priežiūros elementais – laparoskopine operacijos technika, anestezijos metodais, širdies ir kvėpavimo funkcijų neinvazinės stebėsenos technikomis, pooperacinės priežiūros ypatumais, t. y. naudojamos kompleksiškai, gali pagerinti ne tik paciento būklės valdymą operacijos metu, bet ir palengvinti sveikimą po operacijos.

2. DARBO TIKSLAS

Nustatyti ir palyginti bendrosios endotrachėjinės ir kombinuotos endotrachėjinės epiduralinės anestezijos įtaką atskiroms organų sistemoms ir tas sistemas apibūdinantiems rodikliams laparoskopinių kolorektalinių operacijų metu.

3. DARBO UŽDAVINIAI

1. Nustatyti hemodinamikos ir kvėpavimo sistemos parametrų kitimo tendencijas pacientams, kuriems atliekamos laparoskopinės storosios žarnos operacijos, taikant bendrąją ir kombinuotą anestezijos metodus.
2. Palyginti perioperacinės analgezijos būdus, taikomus atliekant laparoskopines storosios žarnos operacijas.
3. Palyginti infuzinės terapijos apimtį bei medikamentų, reikalingų hemodinamikos stabilumui užtikrinti, taikymo dažnį bendrosios ir kombinuotos anestezijos atveju pacientams, kuriems atliekamos laparoskopinės storosios žarnos operacijos.
4. Nustatyti anestezijos bei pooperacinio skausmo malšinimo būdų įtaką pacientų trachėjos ekstubacijos laikui, žarnyno motorikos atsinaujinimo greičiui, hospitalizacijos trukmei bei organizmo uždegiminiam atsakui.

4. MOKSLINIS NAUJUMAS

Šiuolaikinėje mokslinėje literatūroje nagrinėjamos kompleksinės metodikos, chirurginės ir anesteziologinės technikos ir pooperacinės priežiūros galimybių pritaikymas greitesniam pacientų sveikimui bei grįžimui prie įprasto gyvenimo. Laparoskopinė kolorektalinė chirurgija ne tik suteikia papildomų galimybių pacientui greičiau pasveikti, bet ir kelia iššūkių bei problemų, susijusių su operacinių veiksnių – ilgalaikio pneumoperitoneumo, nefiziologinės paciento padėties ir kitų, įtaka paciento organizmo sistemoms bei gebėjimui kompensuoti tokius operacinius veiksnius.

Lietuvoje nebuvo nagrinėtos galimybės skirtingomis anestezijos priemonėmis valdyti laparoskopinių kolorektalinių operacijų veiksnius bei sumažinti jų įtaką paciento fiziologinėms sistemoms.

Mokslinėje literatūroje analizuojama anestetikų bei anestezijos būdų įtaka organizmo stresiniam atsakui ir imuninės sistemos moduliacijai. Šiame darbe nagrinėjama epiduralinės analgezijos metodo įtaka organizmo stresiniam atsakui tiriant kortizolio kiekio kitimus ir interleukino-6, kaip vieno pagrindinių uždegimą skatinančių citokinų, koncentracijos kitimą taikant epiduralinę analgezijos metodiką. Pasauliniame

moksliniame kontekste šių tyrimų rezultatai pateikiami prieštaringi, o tokio pobūdžio tyrimų Lietuvoje nebuvo atlikta.

5. PACIENTAI IR METODAI

Gavus Vilniaus regioninio biomedicininių tyrimų etikos komiteto leidimą (pritarimą leidimo papildymui ir leidimą atlikti biomedicininį tyrimą) 2010 05 05 Nr. 158200-05-181-056LP21 (1 priedas), prospektyvinis tyrimas atliktas Vilniaus universiteto Medicinos fakulteto Anesteziologijos ir reanimatologijos klinikos Anesteziologijos, intensyvios terapijos ir skausmo gydymo centre Vilniaus universiteto ligoninėje Santriškių klinikos.

Pacientų randomizacija. Pacientams, kurie pasirašė sutikimą dalyvauti tyrime, buvo paskirtas numeris pagal chronologinę priskyrimo eilę. Šis numeris naudotas pacientui identifikuoti visą tyrimo laiką, tas pats identifikavimo numeris naudotas pirminės apžiūros ir perioperacinio stebėjimo metu bei įkeliant laboratorinių tyrimų duomenis į kompiuterinę duomenų bazę. Visiems atrinktiems pacientams suteiktas mažiausias galimas randomizacijos numeris iš randomizacijos sekos. Randomizacijos seką generavo nepriklausomas statistikas, naudodamas automatizuotą SAS PROC PLAN procedūrą. Atsitiktinės sekos grafikas sudarytas iš vienodo dydžio blokų, kuriuose priskyrimas grupėms atliktas santykiu 1:1 atsitiktine tvarka kiekvienai iš dviejų grupių.

Į tyrimą įtraukti pacientai atsitiktinės atrankos būdu suskirstyti į dvi grupes: intraveninės analgezijos (IVA) ir epiduralinės analgezijos (EA), kurioms numatyta ir taikyta skirtinga analgezijos taktika.

Visiems pacientams, nepriklausomai nuo priskirtosios grupės, skirta vienoda premedikacija midazolamu 0,5 val. iki anestezijos pradžios, pykinimo bei vėmimo profilaktika (8 mg deksametazono), skausmo malšinimas nesteroidiniais vaistais nuo uždegimo (NVNU) – diklofenaku; prehidratacija kristaloidais 10 ml/kg, bendrosios anestezijos indukcija intraveniniu anestetiku (propofoliu) bei vidutinio veikimo raumenų relaksantu (atrakurijumi), anestezijos palaikymui skiriamas tas pats inhaliacinis anestetikas (sevofluranas). Skysčių infuzija operacijos metu palaikyta kristaloidais ir koloidais, o prireikus skiriama efedrino. Operacijos metu stebėtas širdies minutinis tūris ir koreguotas siekiant neleisti paikisti daugiau nei 10 % nuo pradinio. Visi pacientai

operuoti intubavus trachėją tinkamo dydžio endotrachėjiniu vamzdeliu. Patvirtinus vamzdelio padėtį, taikyta dirbtinė plaučių ventiliacija (DPV) kvėpavimo tūrį ir dažnį palaikant pagal EtCO2 rodmenis. Analgezija operacijos metu buvo skiriama pagal poreikį. IVA ir EA grupių pacientams naudoti skirtingi analgezijos metodai: pirmosios grupės – IVA pacientams skiriama intraveninių narkotinių analgetikų (fentanilio, morfino) operacijos metu bei nuolatinė paciento kontroliuojama (PKA) morfino sulfato intraveninė infuzija po operacijos. Antrosios grupės – EA pacientams analgezija užtikrinama epiduriniu metodu. Torakalinis epiduralinis kateteris įkišamas prieš operaciją operacijos dieną; įsitikinus, kad kateterio padėtis taisyklinga (suleidžiant bandomąją lidokaino dozę 1 mg/kg), leidžiamas vietinio anestetiko bupivakaino 0,125–0,25 % tirpalas iki 30 ml tūrio per pusę valandos ir 2 mg (kai paciento svoris mažesnis kaip 50 kg) arba 3 mg (kai svoris didesnis kaip 50 kg) morfino hidrochlorido. Tolesnė analgezija operacijos metu atlikta pagal poreikį epiduriniu metodu. EA grupės pacientams pooperaciniam skausmui malšinti naudota nuolatinė 0,25% bupivakaino su 5 mg morfino hidrochlorido dešimtyje mililitrų epiduralinė infuzija pastoviu greičiu. Abiem grupėms taikytas identiškas gyvybinių funkcijų stebėjimas, atlikti tokie pat tyrimai bei matavimai perioperaciniu laikotarpiu.

Visos operacijos atliktos naudojant vienodą laparoskopinę chirurginę techniką pagal standartizuotą metodiką, laparoskopiškai išpreparuojant reikalingą storosios žarnos dalį (paciento padėtis ant operacinio stalo – ant atitinkamo šono ir žemyn galva), per pjūvį reikalingoje pilvo srityje ištraukiant storosios žarnos dalį, išpreparuojama numatomos anastomozės vieta. Pakitusi žarna rezekuojama, galai sujungiami ir su anastomoze grąžinami į pilvo ertmę (paciento padėtis horizontali). Susiuvama minilaprotominė žaizda, atkuriamas pneumoperitoneumas (paciento padėtis ant operacinio stalo – ant atitinkamo šono ir žemyn galva). Pacientas paguldomas horizontaliai, pašalinami troakarai, susiuvama aponeurozė ties bamba, užsiuvama oda, uždedami tvarsčiai. Po operacijos pacientas perkeliamas į reanimacijos palatą arba reanimacijos ir intensyviosios terapijos skyrių, kur pažadinamas ir ekstubuojamas.

Į tyrimą įtrauktiems pacientams buvo atlikta numatyta pagal diagnozę laparoskopinė storosios žarnos rezekcinė operacija pagal VUL Santariškių klinikų (SK) Pilvo chirurgijos klinikoje patvirtintą metodiką. Priešoperacinis anesteziologo apžiūrėjimas, standartiniai tyrimai iki ir po operacijos pagal VUL SK patvirtintą

metodiką. Tyrimo metu 3 kartus buvo atliekami kortizolio ir interleukino-6 tyrimai kraujyje: prieš anestezijos pradžią, iškart po operacijos ir po 24 valandų nuo pirmojo tyrimo. Statistinei analizei naudoti neinvazinių matavimų duomenys fiksuoti anestezijos metu tam tikrais operacijos etapais: 1- 5 minutės po trachėjos intubacijos, 2- praėjus 15 minučių nuo laparoskopijos pradžios, 3-prėjus10 minučių nuo minilaparotomijos, 4- relaparoskopijos etape, 5- operacijos pabaigoje (užsiuvus odą). Taikyta standartinė pooperacinė priežiūra.

6. REZULTATAI IR JŲ APTARIMAS

Pacientai po operacijos jaučia vidutinį ir stipresnį nei vidutinį skausmą, todėl perioperacinio skausmo valdymo būdo pasirinkimas išlieka aktualus laparoskopinėms kolorektalinėms operacijoms. A.J. Senagore ir kt. (2003) tyrimo rezultatai patvirtino, kad geresnę analgeziją pooperaciniu laikotarpiu galima pasiekti taikant kombinuotą bendrąją endotrachėjinę ir epiduralinę anesteziją. Mūsų atlikto tyrimo duomenimis, EA grupės pacientų analgetikų poreikis buvo statistiškai reikšmingai mažesnis visais vertinimo etapais. Morfino operacijos metu IV grupėje sunaudota triskart daugiau nei EA grupėje, pooperaciniu laikotarpiu – atitinkamai du kartus daugiau. Statistiškai patikimai skyrėsi ir nesteroidinių vaistų nuo uždegimo suvartojimas. Kaip ir G. P. Joshi, F. Bonnet ir H. Kehlet (2013) apžvalgoje, mes taip pat nustatėme, kad nors skausmo lygis ne epiduralinio skausmo valdymo grupių pacientams ir buvo aukštesnis nei epiduralinės grupės, bet visais atvejais neviršijo 4 balų iš 10. Mūsų atliktas tyrimas atskleidžia patikimą pacientų skausmo vertinimo skirtumą tarp grupių. Skausmą iškart po operacijos didesniu nei 3 balai pagal VAS skalę įvertino 25 % IVA grupės ir 5,7 % EA grupės pacientų, o po 24 valandų – atitinkamai 36,1 % IVA grupės ir nė vienas EA grupės. Pasitenkinimą pagal analogišką 10 balų skalę taip pat geriau įvertino EA grupės tiriamieji. Peristaltika iš karto po operacijos nustatyta 52,8 % mūsų pacientų, priklausančių IVA grupei, ir 97,1 % pacientų – EA grupei. Tiriant žarnyno motoriką po paros skirtumo tarp grupių nebuvo: žarnyno peristaltika nustatyta 97,2 % IVA grupės ir 97,1 % EA grupės pacientų. Nagrinėjant intraabdominalinį slėgį laparoskopijos metu kaip galimą įtakos veiksnį pooperacinės motorikos atsinaujinimo greičiui, patikimo skirtumo tarp grupių negauta. Abiejose grupėse IAS vidutiniškai buvo 10–11 mmHg ir

tarp grupių patikimai nesiskyrė abiem laparoskopijos etapais. Šio tyrimo metu gauti duomenys artimi U. Zingg ir kolegų (2009) rezultatams: epiduralinė analgezija atliekant laparoskopines kolorektalines operacijas sumažina opioidų poreikį ir pagreitina žarnyno motorikos atsitaisymą tiek peristaltikos, tiek maisto toleravimo ir pasituštinimo atžvilgiu. Mūsų tyrimo duomenimis, įvertinus laiką iki skysto maisto vartojimo pradžios, didesnio skirtumo tarp grupių nenustatyta, abiejų grupių pacientai pradėjo valgyti vidutiniškai antrą parą po operacijos. Patikimo skirtumo negauta ir analizuojant laiką iki pirmo pasituštinimo. Visi pacientai vidutiniškai pasituštino penktą parą po operacijos.

Darbe nenustatyta statistiškai patikimo skirtumo tarp IVA ir EA grupių pagal komplikacijas.

Mūsų atlikto tyrimo duomenimis, DPV trukmė iki ekstubacijos EA grupės pacientams buvo trumpesnė daugiau nei du kartus, palyginti su IVA grupe. Tai koreliuoja su kitų autorių publikuotais duomenimis. [112, 113, 116, 117, 122, 124, 204, 205] Mūsų atliktas tyrimas parodė, kad dinaminis tampumas statistiškai patikimai tarp IVA ir EA grupių nesiskyrė, išskyrus pradinį matavimą, kuris buvo patikimai mažesnis EA grupėje. Nagrinėjant absoliučius ir santykinius dinaminio tampumo pokyčius nustatyta, kad EA grupės pacientai patyrė mažesnį maksimalų slėgį kvėpavimo takuose, dėl to šios grupės pacientų dinaminio tampumo pokyčiai buvo mažesni nei IVA grupės. Kitos sąlygos tyrimo metu buvo standartizuotos abiem grupėms: intraabdominalinis slėgis patikimai nesiskyrė. Paciento padėties – Trendelenburgo su pavertimu ant šono pagal operacijos metodiką – trukmė ir operacijos trukmė IVA ir EA grupėse patikimai nesiskyrė. Nors minutinės ventiliacijos reikšmių skirtumas nustatytas nuo minilaparotomijos etapo, abiejų grupių minutinės ventiliacijos absoliučių ir santykinių reikšmių pokyčio negauta. Didžiausio slėgio kvėpavimo takuose reikšmės atskirais laparoskopinės operacijos etapais labiau nesiskyrė, bet statistiškai patikimai skyrėsi tiek absoliutus, tiek santykinis pokytis tarp IVA ir EA grupių. Analogiškai skyrėsi santykiniai didžiausio slėgio kvėpavimo takuose pokyčio dydžiai abiejų laparoskopijų metu, t. y. EA grupės didžiausio slėgio pokyčiai buvo mažesni už analogiškus IV grupėje. Laparoskopinių storosios žarnos operacijų metu diafragmos judesius riboja dėl pneumoperitoneumo padidėjęs intraabdominalinis slėgis ir paciento Trendelenburgo padėtis.

Vienas iš pagrindinių neinvazinio širdies ir kvėpavimo funkcijų stebėjimo sistemos, paremtos Ficko kartotinio įkvėpimo metodu, trūkumų yra tai, kad pacientas turi padėti, jei tyrimas vykdomas jam esant sąmoningam (Širvinskas E ir kt., 2005). Mūsų tyrime visi parametrai matuoti tik DPV sąlygomis. Įvertinus, kad CO2 rezorbcija laparoskopijos metu pacientams gali skirtis ir įtakoti NICO pateikiamus rezultatus, analizuoti ir lyginti santykiniai dydžiai bei tų dydžių pokyčiai.

Laparoskopijos metu hemodinamikos svyravimus visų pirma sukelia dėl pneumoperitoneumo padidėjęs intraabdominalinis slėgis. Pirmosios laparoskopijos metu vidutinis arterinis kraujospūdis (VKS) IVA ir EA grupių pacientų skyrėsi patikimai, kaip ir SKS bei DKS. Šiuo operacijos etapu patikimai skyrėsi ir absoliutus bei santykinis VKS pokytis. Širdies susitraukimų dažnis, tiek absoliutaus bei santykinio pokyčio skirtumas tarp grupių, nustatytas minilaparotomijos etape, nesutapo su kraujospūdžio pokyčiais. Sistolinio tūrio, minutinio širdies tūrio ir širdies indekso absoliučių dydžių pokyčiai neparodė patikimų ar su VKS pokyčiais susijusių skirtumų, lyginant IVA ir EA grupių hemodinamikos pokyčius. Mūsų tyrimo duomenys ŠSD absoliutų ir santykinį patikimą skirtumą tarp tyrimo grupių parodė tik minilaparotomijos metu. Absoliučios ŠSD reikšmės IV ir EA grupių pacientų nesiskyrė. Nagrinėjant širdies minutinio tūrio, širdies indekso ir širdies sistolinio tūrio kitimus, nustatytas patikimas visų trijų parametrų santykinio pokyčio skirtumas tarp grupių ne tik atliekant minilaparotomiją, bet ir kitais operacijos etapais – relaparoskopijos ir užsiuvimo, kuris nekoreliavo su ŠSD santykiniu pokyčiu. Todėl daryta išvada, kad tokių santykinių pokyčių skirtumų priežastis galėjo būti bendrosios anestezijos ir epiduralinės blokados poveikis efektyviai blokuojant simpatinės nervų sistemos atsaką į ilgalaikį pneumoperitoneumą bei kitus operacinius veiksnius. Tokią prielaidą patvirtina ir kitų mokslininkų atlikti tyrimai [Shin ir kt., 2013, Rist M ir kt., 2001).

Palyginę infuzinės terapijos tirpalus, efedrino poreikį anestezijos metu, diurezę perioperaciniu laikotarpiu, nustatėme, kad abiejų grupių pacientams sulašintų kristaloidų kiekis ir diurezė pirmą pooperacinę parą statistiškai patikimai nesiskyrė. Efedrino ir koloidų EA grupės hemodinamikai palaikyti reikėjo statistiškai patikimai daugiau, tačiau tai neturėjo įtakos inkstų funkcijai, abiejų grupių pacientų diurezė tiek operacijos metu, tiek pirmą pooperacinę parą statistiškai patikimai nesiskyrė.

Mūsų tyrimas parodė, kad epiduralinės analgezijos grupės pacientams kortizolio koncentracijos didėjimas po operacijos kraujo serume buvo patikimai mažesnis nei bendrosios anestezijos grupės, t. y. EA grupės pacientų stresinis organizmo atsakas mažesnis nei IVA grupės, geresnė skausmo kontrolė pooperaciniu laikotarpiu ir palankesnis pacientų vertinimas. Mokslinėje literatūroje uždegimo atsakas dėl laparoskopinių storosios žarnos rezekcinių operacijų nėra plačiai tyrinėtas, nurodoma, kad reikia toliau tirti interleukinų koncentracijos kitimus.

Paskelbtuose moksliniuose tyrimuose nurodoma, kad uždegimą skatinančių interleukinų kiekiui perioperaciniu laikotarpiu gali turėti įtakos operacinės traumos dydis bei anestezijos metodas (Hu JK ir kt., 2003, Moselli NM ir kt., 2011, Menges P ir kt., 2012). Kai kurie tyrėjai nurodo nustatyto interleukinų kiekio ir skausmo koreliaciją (Watkins LR ir kt., 1995, Watkins LR ir kt., 1999, Kuo CP ir kt., 2006), epiduralinės analgezijos ir mažesnio uždegimo atsako koreliaciją (Moselli NM ir kt., 2011, Menges P ir kt., 2012, Kuo CP ir kt., 2006, Ahlers O ir kt., 2008, Beilin B ir kt., 2003, Hong JY, Lim KT, 2008), mažesnį komplikacijų skaičių perioperacinei analgezijai taikant epiduralinį metodą (Moselli NM ir kt., 2011). Mūsų duomenimis, nė vienoje grupėje nerasta koreliacijos tarp skausmo įvertinimo ir interleukino-6 koncentracijos kraujo serume, epiduralinės analgezijos ir interleukino-6 koncentracijos kitimo po operacijos skirtumo. Nustatėme operacijos trukmės ir interleukino-6 koncentracijos koreliaciją po operacijos nepriklausomai nuo naudoto analgezijos metodo, o tai rodytų interleukino-6 koncentracijos ir operacinės traumos poveikio sąryšį. Komplikacijų skaičius nesiskyė pagal taikytą perioperacinio skausmo valdymo būdą. ANOVA analizės metodu IVA grupės pacientams nustatyta koreliacija tarp interleukino-6 kiekio kraujo serume po 24 valandų nuo pirmo tyrimo ir komplikacijų išsivystymo.

Atliekant planines kolorektalines operacijas, CRB tyrimas gali būti naudingas infekcinių komplikacijų išsivystymo kontrolei (MacKay GJ, 2011). Mūsų tyrimo metu nenustatyta patikimo CRB koncentracijos kraujo serume skirtumo tarp EA ir IVA grupių nei pirmas tris paras, nei praėjus 4 ar 6 paroms po operacijos. Koreliacija siejo CRB koncentraciją ir komplikacijų pasireiškimą visoje tiriamųjų grupėje bei IVA grupėje tiek per pirmas tris dienas (imtas vidurkis), tiek po 4 bei 6 dienų. Tačiau EA grupėje tokia koreliacija tarp komplikacijų ir CRB koncentracijos nustatyta tik praėjus 6 paroms po operacijos. G. J. MacKay ir kt. (2011) atliktame tyrime nurodoma komplikacijų atžvilgiu

saugi CRB koncentracija – mažiau nei 145 mg/ml ketvirtą parą po operacijos; saugią 140 mg/ml koncentraciją nurodo T. Welsch ir bendraautoriai (2007), tačiau abi minėtos studijos atliktos operuojant atviruoju būdu. Mūsų tiriamiesiems CRB po 4 dienų 102,5±78,9 mg/l jau rodė esant komplikacijas nepriklausomai nuo naudoto analgezijos metodo. Kai kurie autoriai teigia, kad operuojant laparoskopine metodika sukeliamas organizmo uždegimo atsakas, kuris pagal CRB ir IL-6 reikšmes nesiskiria nuo atvirųjų metodikų. Tai aiškinama chirurginiu žarnos vientisumo suardymu, kuris bendras abiem operacijų metodikoms (Tang CL ir kt.2001, Fukushima R it kt. 1996, Dunker MS ir kt. 2003)

7. IŠVADOS

1. Kombinuotos endotrachėjinės epiduralinės anestezijos grupės pacientų hemodinamikos svyravimai buvo mažesni.

Taikant epiduralinę blokadą laparoskopinėms kolorektalinėms operacijoms, dinaminio tampumo pokytis (sumažėjimas) dėl DPV ir intraabdominalinio slėgio sąveikos buvo mažesnis.

2. Analgezijai pasitelkiant epiduralinį skausmo malšinimo metodą, perioperacinis pacientų skausmo valdymas ir pasitenkinimas yra geresnis.

3. Kristaloidų infuzinės terapijos apimtis nesiskyrė tarp skirtingų analgezijos metodų grupių. Koloidų ir efedrino poreikis skausmo valdymui buvo dažnesnis naudojant epiduralinį analgezijos metodą.

4. 4.1. Trachėjos ekstubacijos laikas kombinuotos endotrachėjinės epiduralinės anestezijos grupės pacientams buvo statistiškai patikimai trumpesnis.

4.2. Žarnyno peristaltikos atsitaisymas EA grupėje buvo patikimai ir daug ankstyvesnis nei IVA grupės.

4.3. Naudojant epiduralinę analgeziją laparoskopinei kolorektalinei chirurgijai, sukeliamas mažesnis stresinis organizmo atsakas – kortizolio koncentracijos padidėjimas, ir nenustatyta patikimo komplikacijų padaugėjimo. Taikant kombinuotą endotrachėjinę epiduralinę anesteziją, kortizolio koncentracijos augimas iškart po operacijos buvo mažesnis. Mūsų duomenimis, IL-6 koncentracijos didėjimas koreliuoja su operacijos trukme, o ne su analgezijos metodu. Nenustatėme reikšmingų CRB koncentracijos pokyčių dėl analgezijos metodo poveikio.

4.4. Neįrodyta analgezijos būdo įtaka pacientų gydymo ligoninėje trukmei, skysto maisto vartojimo pradžios greičiui bei pirmo pasituštinimo po operacijos laikui.

8. PRAKTINĖS REKOMENDACIJOS

1. Kombinuota endotrachėjinė epiduralinė anestezija yra tikslinga atliekant laparoskopines storosios žarnos operacijas, nes padeda mažinti stresinį organizmo atsaką, gerai valdyti pooperacinį skausmą ir suteikia pacientams geresnį pasitenkinimą.

2. Kombinuota endotrachėjinė epiduralinė anestezija tinkama taikant greitesnio sveikimo protokolą kolorektalinėje chirurgijoje, nes ji neilgina pooperacinio pacientų gydymo ligoninėje bei nedidina komplikacijų skaičiaus.