GODIŠNJI IZVJEŠTAJ MENTORA O NAPREDOVANJU DOKTORANDA

Akademska godina za koju se podnosi izvještaj	2022./2023.		
OPŠTI PODACI O DOKTORANDU			
Titula, ime, ime roditelja, prezime	Ognjenka (Predrag) Šarenac, dr med.		
Fakultet	Medicinski fakultet UCG		
Studijski program	Doktorske studije - medicina		
Broj indeksa	8/07		
MENTOR/MENTORI			
Prvi mentor	Akademik Ranko Lazović	Medicinski fakultet UCG; Crna Gora	Hirurgija
Drugi mentor	Prof. dr Ivan Palibrk	Medicinski fakultet Univerziteta u Beogradu, Srbija	Anesteziologija sa reanimatologijom

EVALUACIJA DOKTORANDA*					
Koliko ste zadovoljni kvalitetom održanih susreta sa doktorandom?	☐1	☐2	☐3	☐4	☒5
/					
Da li je definisan plan rada sa doktorandom?	☒DA	☐NE			
Da li je doktorand ostvario napredak prema predviđenom planu rada?	☒DA	☐NE			
/					
Kvalitet napretka doktorandovog istraživačkog rada u periodu između dva izvještaja je:	☐1	☐2	☐3	☐4	☒5
/					
Dati ocjenu doktorandove spremnosti za konsultacije.	☐1	☐2	☐3	☐4	☒5
Dati ocjenu planiranja i izvršavanja godišnjih istraživačkih aktivnosti i stručnog usavršavanja doktoranda.	☐1	☐2	☐3	☐4	☒5
Dati ocjenu napretka u savladavanju metodologije naučno-istraživačkog rada.	☐1	☐2	☐3	☐4	☒5
Dati ocjenu o aktivnostima sprovedenim na pisanju i objavljivanju naučnih radova.	☐1	☐2	☐3	☐4	☒5
Dati ocjenu doktorandovog generalnog odnosa prema studijama.	☐1	☐2	☐3	☐4	☒5
Dati ocjenu ukupnog kvaliteta doktorandovog rada.	☐1	☐2	☐3	☐4	☒5

*Ocjene su: 1 – nedovoljan, 2 – dovoljan, 3 – dobar, 4 – vrlo dobar, 5 – odličan

/
SAGLASNOST ZA NASTAVAK STUDIJA

Može li doktorand nastaviti studije?	☒ Da ☐ Da, uz određene uslove ☐ Ne

/
Napomene
/
IZJAVA MENTORA

Doktorantkinja je u fazi izrade pisanog dijela rada. Završetak doktorske disertacije i javna odbrana planirani su za prvu polovinu 2023. godine; što je u saglasnosti sa gantogramom priloženim uz prvi izvještaj mentora.
U međuvremenu, kandidatkinja je objavila jedan rad iz doktorske disertacije; pod nazivom „Impact of Perioperatively Administered Amino Acids, Lidocaine, and Magnesium on Inflammatory Response and Pain Associated with Abdominal Surgery: A Prospective Clinical Study" u renomiranom međunranodnom časopisu sa otvorenim pristupom Medical Science Monitor; koji se nalazi na SCIE listi i pripada Q2 kategoriji; sa impakt faktorom 3.386.
Shodno navedenom, saglasni smo da kandidatkinja nastavi izradu svoje doktorske disertacije.

1. Sarenac O, Lazovic R, Vukcevic B, Lazovic J, Palibrk. I Impact of Perioperatively Administered Amino Acids, Lidocaine, and Magnesium on Inflammatory Response and Pain Associated with Abdominal Surgery: A Prospective Clinical Study. Med Sci Monit. 2022 (In press); doi: 10.12659/MSM.939204

U Podgorici,
9.1.2023.

Akademik Ranko Lazović

Prof. dr Ivan Palibrk

Prilog dokumenta sadrži:

- Gantogram aktivnosti (za prvi izvještaj mentora)
- Objavljeni rezultati rada na izradi doktorske disertacije (za drugi izvještaj mentora)

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Impact of Perioperatively Administered Amino Acids, Lidocaine, and Magnesium on Inflammatory Response and Pain Associated with Abdominal Surgery: A Prospective Clinical Study

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: Abdominal surgery is associated with a systemic inflammatory response which facilitates postoperative complications through immune imbalance and hypercatabolism. The aim of the study was to evaluate the effect of the combined perioperative lidocaine, magnesium, and amino acids on postoperative inflammation and pain.

Material/Methods: This prospective, randomized, double-blind study included 2 groups of patients undergoing abdominal surgery: Group 1 – receiving the aforementioned substances; and Group 2 – control (undergoing conventional general anesthesia). The following parameters were evaluated intraoperatively: arterial blood pressure, end-tidal CO_2 level, urine output, bispectral index, base excess, oxygen saturation, operating room temperature and body temperature (BT), opioid use, and surgery duration; and postoperatively: total leukocyte (WBC), neutrophil, lymphocyte and platelet count; fibrinogen, C-reactive protein (CRP), procalcitonin (PCT) and interleukin (IL)-6 levels; numeric rating scale (NRS) pain level, first flatus and bowel movement, and postoperative complications. The postoperative parameters were evaluated 2 h and 6 h postoperatively, as well as on postoperative days (POD) 1, 2, 3, and 5.

Results: Group 1 showed lower counts of WBC, neutrophils, and lymphocytes and lower fibrinogen, CRP, PCT, IL-6, and BT in the first 5 POD, as well as NRS scores and time to first flatus/bowel movement. The groups did not differ significantly regarding postoperative complications.

Conclusions: The isolated effects of lidocaine, magnesium, and amino acids in surgery have been described previously. To the best of our knowledge, this is the first study to show the anti-inflammatory and analgesic effects of simultaneous use of these substances in abdominal surgery.

Keywords: **Amino Acids • General Surgery • Lidocaine • Magnesium**

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Background

Surgery is associated with local tissue damage and alterations in the physiological mechanisms of homeostasis [1,2]. SIRS (systemic inflammatory response syndrome) occurs in 16% to 89% of abdominal surgical patients [3-5]. IL-6 (interleukin-6) is the key proinflammatory cytokine, responsible for the activation of acute phase reactants CRP (C-reactive protein) and PCT (procalcitonin) [5]. PCT [6] and IL-6 [1,7,8] levels are directly correlated with the intensity of surgical trauma.

Postoperative pain involves a combination of inflammatory and neuropathic mechanisms, both associated with hyperalgesia. The imperative of fast-track protocols is adequate analgesia with few adverse effects, enabling the patient to function independently and to be discharged sooner [9]. Effective multimodal analgesia which reduces the need for opioid drugs is one of the key elements in ERAS (enhanced recovery after surgery) protocols [10].

Lidocaine, a local anesthetic drug, blocks the sodium-potassium channel [11], thus alleviating postoperative pain [12-16] through the following mechanisms: analgesic, anti-hyperalgesic, and anti-nociceptive [17]. Furthermore, lidocaine serves as a N-methyl-D-aspartate (NMDA) receptor antagonist [18]. Perioperatively administered lidocaine also has anti-inflammatory activity [17,19-24] and facilitates the return of bowel function after abdominal surgery [9,16,23,25].

Perioperative amino acid solutions have a positive thermogenic effect [26-28] and anti-inflammatory activity [29-31] in surgical patients.

Magnesium is a NMDA receptor antagonist (as is lidocaine) [32], central nervous system depressor (through the effect on calcium channels), and sodium-potassium gate modulator [33]. There is evidence of its analgesic [32-36] and anti-inflammatory effect [37,38] in surgical patients.

The reduced postoperative systemic inflammatory response decreases the risk of postoperative complications through alleviation of immune system dysregulation and hypercatabolism. The aforementioned studies most commonly described the separate effects of lidocaine, magnesium, and amino acids on postoperative inflammatory response or pain. The aim of the present study was to examine the influence of simultaneously administered amino acids, lidocaine, and magnesium on postoperative inflammatory response and pain in abdominal surgery.

Material and Methods

Ethics Statement

This prospective, double-blind study was conducted from September 2021 to August 2022 on 100 patients (divided into 2 groups of 50 patients each) treated in the Clinical Center of Montenegro (Podgorica, Montenegro). The study was approved by the Ethics Committee of the Clinical Center of Montenegro (03/01-6031/1). The research was conducted in accordance with the Declaration of Helsinki. Every patient signed the written informed consent form before inclusion.

Inclusion Criteria

This prospective, randomized, double-blind study included 2 patient groups: Group 1 was the experimental group (receiving amino acids, lidocaine, and magnesium perioperatively, along with the conventional anesthesia procedures) and Group 2 was the control group (undergoing conventional anesthesia). The research was conducted on patients of both sexes, age 35-75 years, undergoing 1 of the following surgical procedures in general anesthesia: total/subtotal gastrectomy, small bowel resection and anastomosis, right/extended right/left/subtotal/total colectomy and anastomosis; or high anterior/low anterior resection.

Exclusion Criteria

1. Associated malignant disease (excluding the disease for which the patient underwent the abdominal operation);
2. Autoimmune disorders, congenital/acquired immunodeficiency;
3. Previous/current immunomodulatory therapy;
4. Emergency conditions (due to the initial systemic inflammatory response);
5. Postoperative complications altering the inflammatory response (eg, infections, anastomotic leak);
6. Previous allergy to any of the substances used in the study.

The Anesthesia Protocol

All patients were preoperatively examined and prepared for surgery by an anesthesiologist according to the comorbidities and the planned intervention according to the local protocol. The patients were rehydrated during the day before surgery by drinking water or tea, as well as intravenous 1000 ml Ringer-lactate and 1000 ml 5% dextrose solution with or without 6 international units of rapid-acting insulin (adjusted according to glycemia levels in diabetic patients). Solid foods were not consumed within 24 h before surgery and liquids (including high-calorie liquid foods) were not consumed within 4 h before surgery. The patients were administered 1 mg oral alprazolam 6 h

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before surgery and 40 mg i.v. pantoprazole 1 h before surgery. The antibiotic prophylaxis with first-generation cephalosporin and metronidazole was conducted 60 min before the incision was made. In case of antibiotic allergy, 600 mg i.v. clindamycin and 240 mg i.v. gentamycin were used. All patients received low-molecular-weight heparin 12 h before surgery (dose adjusted to body mass and comorbidities).

The patients in both groups underwent intravenous anesthesia induction and maintenance, with previous use of 100% oxygen. Propofol 2-2.5 mg/kg was administered, as well as 5 mcg/kg fentanyl and 0.2 mcg/kg cisatracurium. Tracheal intubation was performed using an endotracheal tube with cuff. A nasogastric tube and a central venous catheter were inserted. Invasive arterial pressure monitoring was used. Body temperature (BT) was measured using a nasopharyngeal temperature probe. Hourly urine output was monitored. A Primus® (Draeger) ventilator was used. Mechanical ventilation was pressure-balanced (5 mmHg positive end-expiratory pressure (PEEP), 7 mmHg pressure support, 20 mmHg peak inspiratory pressure (PIP), and breath rate 10-12/min). End-tidal CO_2 (EtCO2) levels were in the normocapnia range (30-45 mmHg). Anesthesia maintenance was achieved using hypnotic volume concentrations of sevoflurane (0.7%), while the anesthesia was opioid-based. Muscle relaxation was maintained with bolus infusions of cisatracurium. We administered 7-10 mg intravenous morphine approximately 40 min before the end of surgery. At the end of the procedure, the neuromuscular blockade was reversed (using 2.5 mg neostigmine and 1 mg atropine. Bispectral index (BIS) was maintained at 40-60.

During surgery, fluid and electrolyte resuscitation, as well as blood transfusion and blood products, were administered based on the full blood count, coagulation factor levels and clotting time, hemodynamic and EtCO2 monitoring changes, urine output, and the occurrence of intestinal edema and conjunctival suffusion. Also, visible blood loss was monitored, and the insensible fluid losses were estimated. All intravenous infusions were heated to 37°C. Patients were covered with regular sterile blankets (without heating) during surgery.

All patients received the same postoperative analgesic and antiemetic therapy (24-h i.v. infusion of 300 mg tramadol, 5 mg metamizole-sodium, and 3 mg ondansetron in 500 ml 0.9% saline, administered at an average rate of 25 ml/h). Based on the clinical signs and the patient's subjective perception, an additional bolus of 2 mg i.v. morphine was used in case of pain degree > 5 on the numeric rating scale (NRS). CPAP (continuous positive airway pressure) ventilation was used during the first 2 postoperative hours in all patients to prevent lung atelectasis. Verticalization was initiated 6-8 h postoperatively.

Randomization and Study Protocol

We prepared 50 cards marked "Group 1" and 50 cards marked "Group 2" before the beginning of the study. Before the procedure start time, the researcher pulled a card for the specific patient and gave it to the anesthetist in the preoperative unit, who then prepared the appropriate solutions.

Based on the card pulled for the specific patient, the anesthetist in the preoperative unit prepared the solutions and gave them to the anesthetist in the operating room (OR). Thus, the researcher, as well as the anesthesiologist and the anesthetist treating the patient in the OR, did not know which group the patient was in. In the event of allergy and other unexpected events, the group was revealed and the patient was excluded from the study.

Patients in Group 1 received additional i.v. 2% lidocaine: 100 mg diluted in 100 ml 0.9% saline infused over 30 min before the incision (at a rate of 200 ml/h). This was followed by 300 mg i.v. lidocaine diluted in 300 ml 0.9% saline administered during the procedure at a rate of 250 ml/h, and this was discontinued after infusion termination. The maximum lidocaine dose did not exceed 300 mg/h. Also, Group 1 received i.v. 1% magnesium-sulphate (2 g diluted in 100 ml 0.9% saline infused over 20 min before the incision); as well as i.v. 10% amino acid solution Aminosol® (manufactured by Hemomont, Podgorica, Montenegro) administered after the induction of anesthesia as 500-ml infusions at a maximum rate of 250 ml/h until the end of surgery (the maximum dose being 2 g/kg). Aminosol® contains the following amino acids: isoleucine, leucine, valine, lysine, methionine, threonine, phenylalanine, alanine, arginine, glycine, histidine, proline, serine, tyrosine, taurine, and tryptophan [39].

The patients in Group 2 received 100 ml 0.9% saline administered 30 min before incision (at a rate of 200 ml/h), 300 ml 0.9% saline administered during surgery at a rate of 250 ml/h, 100 ml 0.9% saline infused over 20 min before the incision, 500 ml 0.9% saline administered during surgery and after induction of anesthesia as a 500-ml infusion at a maximum rate of 250 ml/h until the end of surgery, as per the regimen used in Group 1. All intravenous fluid containers were marked such that the anesthesiologist and the anesthetist in the OR were unaware of their contents.

The following parameters were measured:

1. Preoperative: sex, age, body weight, height, body mass index (BMI), comorbidities, indication for surgery, preoperative total leukocyte (WBC), neutrophil, lymphocyte, and platelet (PLT) count, and levels of fibrinogen, CRP, IL-6, and PCT, assessed at 6 AM the day before surgery).

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Table 1. Preoperative parameters in Group 1 and Group 2 (statistically significant differences are in bold; $P<0.05$).

Parameter	Group 1 (n=50)	Group 2 (n=50)	*p*-value
Sex (n (%))			
Male	30 (60.0)	25 (50.0)	
Female	20 (40.0)	25 (50.0)	0.315*
Age in years (mean (SD))	61.71±9.61	63.72±11.30	0.452**
Indication for surgery (n (%))			
Rectal cancer	20 (40.0)	21 (42.0)	
Ovarian cancer	2 (4.0)	1 (2.0)	
Colon cancer	12 (24.0)	7 (14.0)	
Hepatocellular carcinoma	3 (6.0)	7 (14.0)	
Pancreatic cancer	3 (6.0)	4 (8.0)	
Gastric cancer	4 (8.0)	3 (6.0)	
Carcinoma of the small intestine	1 (2.0)	2 (4.0)	
Other	5 (10.0)	5 (10.0)	0.792*
Body weight (kg) (mean (SD))	80.12±20.563	76.50±15.73	0.497**
Body height (cm) (mean (SD))	173.45±6.87	172.20±6.77	0.395**
BMI (kg/m^2) (mean (SD))	26.77±6.66	25.67±4.47	0.795**
WBC count (10^9/l) (mean (SD))	7.79±3.30	8.49±3.15	0.215**
Neutrophil count (10^9/l) (mean (SD))	5.57±3.20	6.23±2.73	0.089**
Lymphocyte count (10^9/l) (mean (SD))	1.51±1.67	1.18±0.71	0.181**
PLT count (10^9/l) (mean (SD))	259.63±75.37	225.00±107.43	**0.030****
Fibrinogen level (g/l) (mean (SD))	3.57±0.95	3.40±1.09	0.359**
CRP level (mg/l) (mean (SD))	29.53±41.88	47.72±60.35	0.055**
IL-6 level (pg/ml) (mean (SD))	48.10±37.92	107.76±188.05	**0.005****
PCT level (ng/ml) (mean (SD))	0.29±0.46	0.27±0.41	0.988**

* Chi-squared test; ** Mann-Whitney U-test.

2. Intraoperative: arterial blood pressure (BP), EtCO2, urine output, BIS, peripheral arterial oxygen saturation, and base excess (from the arterial blood gas analyses) were assessed at the induction of anesthesia (marked superscript "A") and again after the removal of the specimen (marked superscript "B" in the Results section). Temperature in the operating room (TOR) and body temperature (BT) were assessed at the induction (marked superscript "A"), after the removal of the specimen (marked superscript "B") and at the end of the operation (marked superscript "C" in the Results section). We also assessed the amount of opioid analgesic used throughout the operation, as well as the operation duration.
3. Postoperative: WBC, neutrophil, lymphocytes, PLT count, fibrinogen, CRP, PCT, IL-6 levels, axillary BT, and pain intensity before analgesic therapy as evaluated with NRS (0-10).

The aforementioned postoperative parameters were measured 6 times for each patient:

1. 2 h postoperatively (marked "1");
2. 6 h postoperatively (marked "2");
3. Postoperative day (POD) 1 at 6 AM (marked "3");
4. POD 2 at 6 AM (marked "4");
5. POD 3 at 6 AM (marked "5");
6. POD 5 at 6 AM (marked "6" in the Results section).

Furthermore, the POD of the first postoperative flatus or bowel movement was registered for each patient, as well as the occurrence of postoperative surgical complications according to the Clavien-Dindo classification [40].

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Table 2. Comorbidities in Group 1 and Group 2.

Comorbidities (n (%))	Group 1 (n=50)	Group 2 (n=50)	*p*-value
Yes	40 (80.0)	36 (72.0)	
No	10 (20.0)	14 (28.0)	0.349*
Comorbidities (listed)			
Abdominal aortic aneurysm	0 (0)	1 (2.0)	
Atrial fibrillation	1 (2.0)	2 (4.0)	
Anemia	5 (10.0)	2 (4.0)	
Liver cirrhosis	0 (0)	2 (4.0)	
Cardiomyopathy	1 (2.0)	2 (4.0)	
Depression	1 (2.0)	1 (2.0)	
Diabetes	8 (16.0)	9 (18.0)	
Chronic obstructive pulmonary disease	5 (10.0)	3 (6.0)	
Arterial hypertension	14 (28.0)	19 (38.0)	
Hyperthyroidism	1 (2.0)	0 (0)	
Obesity	4 (8.0)	1 (2.0)	
Parkinson's syndrome	0 (0)	1 (2.0)	
Multiple sclerosis	0 (0)	1 (2.0)	
Angina pectoris	1 (2.0)	0 (0)	
Hashimoto thyroiditis and hypothyroidism	0 (0)	1 (0)	0.383*

* Chi-squared test.

Statistical Analysis

Statistical analysis was performed using descriptive and analytical statistics. Categorical variables were compared using the chi-squared test. The normality of distribution was assessed using the Kolmogorov-Smirnov test. Continuous variables not normally distributed were compared using the Mann-Whitney U test. As an additional analysis, the receiver-operating characteristic (ROC) curve with the calculation of the area under the curve (AUC) was used to indirectly assess the possible association of amino acids, lidocaine, and magnesium use with the levels of the postoperative inflammatory and pain parameters. SPSS software for Windows 22.0 was used. $P<0.05$ was considered statistically significant.

Results

Preoperative Data

The groups did not differ significantly by sex, age, indications for surgery, or other preoperative parameters excluding the PLT count (higher in Group 1) and IL-6 level (lower in Group 1). The most common indication for surgery in both groups was rectal cancer (**Table 1**).

Arterial hypertension was the most common comorbidity in both groups. The groups did not differ significantly by comorbidities (**Table 2**).

Intraoperative Data

Intraoperative data are presented in **Table 3**. EtCO2 and base excess were significantly different between Groups 1 and 2, as well as the BT[B] and TOR[A-C].

Intraoperative opioid usage was not different between Groups 1 and 2 (969.00±222.67 vs. 915.00±163.90, $P=0.545$; average doses expressed in micrograms).

Postoperative Data

Postoperative variations of cellular counts; fibrinogen, CRP, PCT, and IL-6 levels, as well as axillary BT and NRS scores, are presented in **Figures 1-3**.

First flatus usually occurred on POD 2 (2.12±0.59 days) in Group 1 and POD 4 in Group 2 (4.16±1.02 days). First stool occurred usually on POD 3 (3.18±0.80 days) and POD 6 (6.40±1.29 days)

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Table 3. Intraoperative parameters of Group 1 and 2 (statistically significant differences are in bold; *P*<0.05).

Parameters (mean (SD))	Group 1 (n=50)	Group 2 (n=50)	*p*-value
BP[A] (systolic) (mmHg)	127.36±10.70	127.20±14.85	0.965*
BP[A] ((diastolic) (mmHg)	79.40±.70	79.00±4.16	0.761*
BP[B] (systolic) (mmHg)	123.98±17.02	126.20±12.27	0.781*
BP[B] (diastolic) (mmHg)	76.72±9.12	77.80±5.82	0.992*
$EtCO_2$[A] (mmHg)	30.08±3.25	32.00±3.93	**0.002***
$EtCO_2$[B] (mmHg)	29.70±3.75	32.86±3.55	**0.001***
Urine output[A] (ml)	89.00±39.50	87.00±66.09	0.225*
Urine output[B] (ml)	501.40±315.90	474.00±267.50	0.895*
BIS[A]	84.80±8.86	82.80±12.30	0.220*
BIS[B]	42.80±11.26	41.20±6.27	0.953*
Oxygen saturation[A] (%)	99.78±1.56	99.90±0.71	0.989*
Oxygen saturation[B] (%)	99.70±2.12	99.90±0.71	0.989*
Base excess[A] (mmol/l)	-2.28±1.18	3.74±1.83	**0.001***
Base excess[B] (mmol/l)	-4.02±1.63	5.24±1.66	**0.001***
Surgery duration (min)	84.80±42.20	81.60±44.14	0.205*
BT[A] (°C)	36.51±0.18	36.48±0.10	0.208*
BT[B] (°C)	36.22±0.50	36.45±0.35	**0.012***
BT[B] (°C)	36.36±0.37	36.49±0.71	0.070*
TOR[A] (°C)	19.26±0.44	19.04±0.20	**0.002***
TOR[B] (°C)	19.26±0.44	19.04±0.20	**0.002***
TOR[C] (°C)	19.22±0.46	19.04±0.20	**0.012***

* Mann-Whitney U-test.

in Groups 1 and 2, respectively. Group 1 showed significantly shorter times to first flatus and stool (*P*<0.001).

ROC curves were used to analyze and compare the AUC of postoperative parameters between Groups 1 and 2, which confirmed the differences listed in **Figures 1-3**. The AUC values are given in **Table 4. Table 5** contains the postoperative complications in Groups 1 and 2 (no significant difference was found regarding the complication occurrence nor the Clavien-Dindo grades).

Discussion

Postoperative pain and ileus are regarded as the most important factors in treatment costs, due to the prolonged hospital stay [9]. Nearly 40% of colorectal surgery patients suffer from postoperative intestinal paresis [10]. Also, a specific problem in abdominal surgery is the occurrence of septic complications, which must be recognized and separated from the postoperative SIRS occurring as an inflammatory response to surgical trauma [41]. Past studies have assessed the influence of inflammatory markers in the discrimination between the physiological inflammatory response and the inflammation accompanying septic complications [42-47].

The research presented herein showed the anti-inflammatory effect of the combination of lidocaine, amino acids, and magnesium in abdominal surgery through lower counts of WBC, neutrophils, and lymphocytes, as well as lower levels of fibrinogen, CRP, PCT, IL-6, and BT, in the first 5 PODs. Furthermore, postoperative pain scores were lower in Group 1. These differences were confirmed with direct comparisons and AUC scores. Intraoperatively, both groups were in the normocapnia range, but Group 1 showed lower deviations in base excess and lower EtCO2, suggesting better oxygenation and, indirectly, a lower production of lactates.

Group 1 showed significantly lower WBC and lymphocyte counts on PODs 1-5, while the neutrophil count was lower on PODs 2-5. Leukocytosis occurs in the first 24 h after surgery, based

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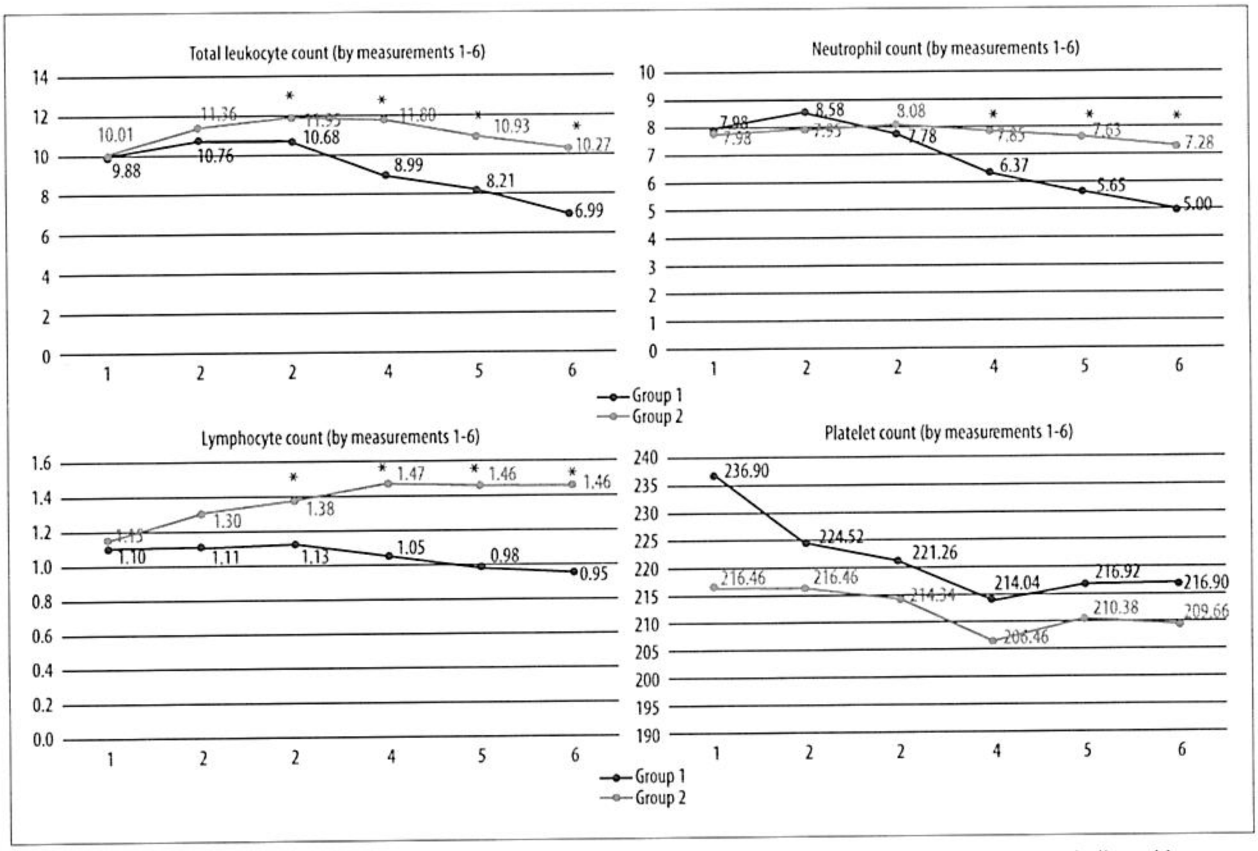

Figure 1. Postoperative WBC, neutrophil, lymphocyte, and PLT counts ($10^9/l$) (statistically significant differences are indicated by an asterisk ($P<0.001$); Mann-Whitney U test).

on neutrophilia. Subsequently, neutrophils are removed from the circulation by the liver, spleen, and bone marrow [2]. PLT counts were higher in Group 1 in all measurements (mirroring the preoperative values), but without statistical significance. Fibrinogen peaked on POD 2 in both groups, with significantly lower levels in Group 1 on PODs 1-5. CRP, PCT, and IL-6 levels were significantly lower in Group 1 in all measurements, peaking on POD 1 in both groups. Group 1 had a significantly lower level of IL-6 preoperatively, which might have influenced postoperative values. However, the reduction of other inflammatory parameters confirms the anti-inflammatory effect of the studied combination of substances. Research on abdominal surgery patients showed a beneficial anti-inflammatory effect of amino acids (mostly glutamine and arginine), leading to lower IL-6 [29,48,49], IL-1, IL-18, TNF (tumor-necrosis factor)-α [29], and CRP levels [30,50,51]. The anti-inflammatory effect of lidocaine is shown by the reduction of postoperative IL-6 and IL-8 [19,22,23], IL-1 [19], and CRP levels [52]. There is limited evidence of the anti-inflammatory effect of magnesium in vascular surgery (lowering the IL-6 level) [37] and in cardiac surgery (lowering the IL-6 and TNF-α levels) [38].

General anesthesia is associated with hypothermia due to a reduction in metabolic thermogenesis, as well as impaired central thermoregulation [53,54]. A systematic review by Aoki et al including 14 randomized clinical trials (RCT) with 626 patients showed a thermogenic effect of perioperative amino acids, as well as faster extubation time and shorter hospital stay [26]. Our study showed intraoperative normothermia in both groups, with the only statistical difference in BT 2, which was lower in Group 1. Therefore, the thermogenic effect of amino acids was not shown. Group 1 had significantly lower postoperative BT in all measurements, most likely due to reduced systemic inflammation.

A Cochrane review from 2015 (45 RCTs, 2802 patients, 25 papers on abdominal surgery, and 20 papers on other surgical areas) showed reduced pain levels and opioid usage (in the first 24 h after surgery) in the group of patients receiving intravenous perioperative lidocaine. This analgesic effect was not shown 48 h after surgery. Lidocaine also reduced the incidence of postoperative ileus (4.8% versus 13.9% in the control group) [9]. Lidocaine is thought to be more effective in abdominal surgery than in other surgeries [55-57], which is somewhat confirmed in the repeated Cochrane review from 2018 (68 RCTs, 4525 patients, 42 papers on abdominal surgery, and 46 papers on other surgical specialties) [58]. This review showed a lower level of evidence of the analgesic and

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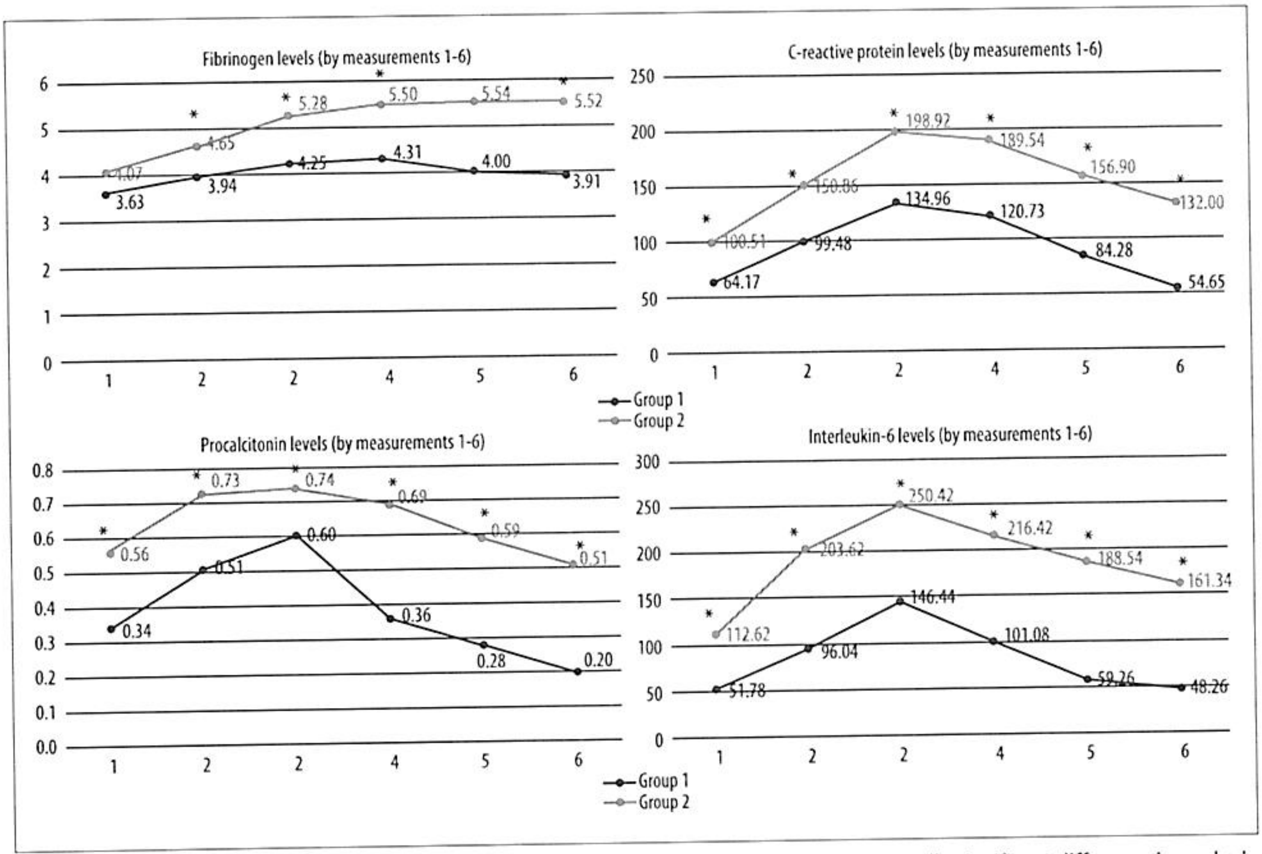

Figure 2. Postoperative levels of fibrinogen (g/l), CRP (mg/l), PCT (ng/ml) and IL-6 (pg/ml) (statistically significant difference is marked with an asterisk (*P*<0.001); Mann-Whitney U test).

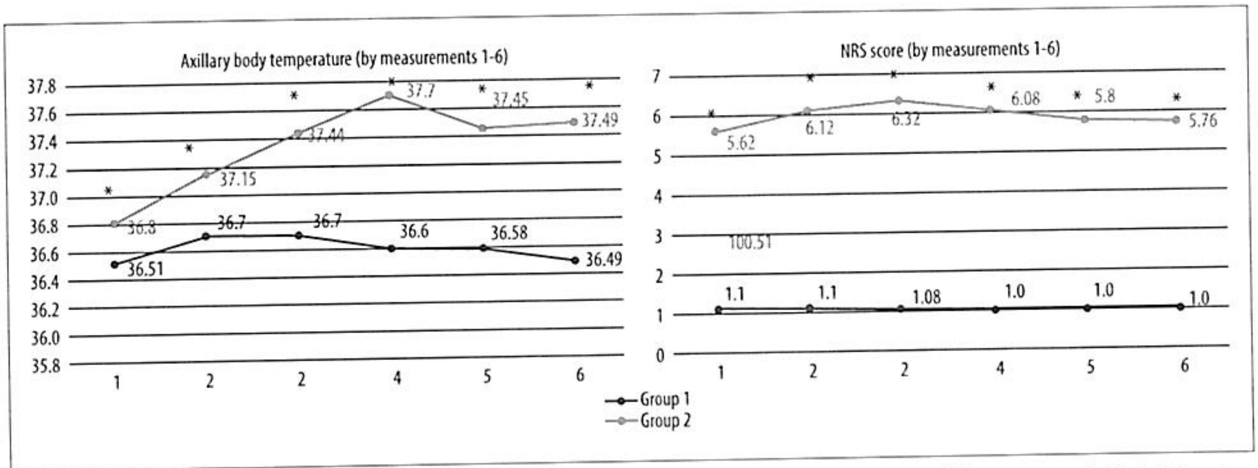

Figure 3. Postoperative axillary BT (°C) and NRS (numeric rating scale) scores (statistically significant differences are indicated by an asterisk (*P*<0.001); Mann-Whitney U test).

prokinetic effect of lidocaine, perhaps due to a higher percentage of non-abdominal surgery papers included in the review. Many studies on lidocaine focused exclusively on pain in the first 24 h [12-14] or 48 h [15] after surgery. The results of studies examining the analgesic effect of lidocaine 72 h after surgery are conflicting [16,59].

Albrecht et al published a meta-analysis in 2013 (25 studies, 1461 patients) showing the effect of perioperative magnesium on reduction of postoperative pain and need for opioid analgesics 24 h after surgery [34], comparable to the meta-analysis by De Oliveira et al from the same year (20 RCTs, 1257 patients) [32]. In 2017, Kim et al compared the effects of lidocaine and magnesium on postoperative pain in 126 patients

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Table 4. ROC curve analysis and AUC calculation of the postoperative statistically significant parameters (excluding the PLT count) (statistically significant differences are in bold; $P<0.05$).

Parameter	Measurement	AUC	p-value
WBC count	1	0.515	0.791
	2	0.559	0.308
	3	0.621	**0.037**
	4	0.700	**0.001**
	5	0.717	**0.001**
	6	0.801	**0.001**
Neutrophil count	1	0.497	0.959
	2	0.492	0.885
	3	0.566	0.257
	4	0.648	**0.011**
	5	0.689	**0.001**
	6	0.743	**0.001**
Lymphocyte count	1	0.529	0.622
	2	0.607	0.066
	3	0.616	**0.045**
	4	0.672	**0.003**
	5	0.694	**<0.001**
	6	0.689	**<0.001**
Fibrinogen	1	0.554	0.356
	2	0.676	**0.002**
	3	0.757	**<0.001**
	4	0.832	**<0.001**
	5	0.909	**<0.001**
	6	0.936	**<0.001**
CRP	1	0.698	**<0.001**
	2	0.704	**<0.001**
	3	0.760	**<0.001**
CRP (continued)	4	0.818	**<0.001**
	5	0.843	**<0.001**
	6	0.881	**<0.001**
PCT	1	0.663	**0.005**
	2	0.721	**<0.001**
	3	0.743	**<0.001**
	4	0.800	**<0.001**
	5	0.802	**<0.001**
	6	0.822	**<0.001**
IL-6	1	0.827	**<0.001**
	2	0.781	**<0.001**
	3	0.779	**<0.001**
	4	0.833	**<0.001**
	5	0.874	**<0.001**
	6	0.894	**<0.001**
BT	1	0.747	**<0.001**
	2	0.770	**<0.001**
	3	0.846	**<0.001**
	4	0.932	**<0.001**
	5	0.936	**<0.001**
	6	0.938	**<0.001**
NRS	1	0.988	**<0.001**
	2	0.989	**<0.001**
	3	0.988	**<0.001**
	4	0.970	**<0.001**
	5	0.970	**<0.001**
	6	0.970	**<0.001**

undergoing mastectomy, showing that the 2 drugs had comparable analgesic effects in the immediate postoperative recovery period, as well as 24 h after surgery [18]. A similar sample was used in a study by Mendonca et al in 2020, which analyzed the combination of lidocaine and magnesium. Their results showed that these 2 drugs combined had superior analgesic effect (in the first 24 h after surgery) compared with the isolated use of lidocaine or magnesium, as well as the control group. The authors suggest that the simultaneous inhibition of NMDA receptors is the foundation of the synergism of these 2 drugs, as well as the attenuation of the membrane potential (modulating the transport of sodium, potassium, and calcium) and their anti-inflammatory effect [33]. Saadawy et al also indicate that combined lidocaine and magnesium might have a prolonged analgesic effect via NMDA receptor inhibition, as well as the prevention of spinal and peripheral hypersensitivity [36].

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Table 5. Incidence of postoperative complications and Clavien-Dindo grades in Groups 1 and 2.

Outcome	Group 1 (n=50) (n (%))	Group 2 (n=50) (n (%))	*p*-value
No complication	45 (90.0)	40 (80.0)	
Complications			
Absolute arrhythmia	1 (2.0)	1 (2.0)	
Basal lung atelectasis	1 (2.0)	0 (0)	
Pleural effusion	2 (4.0)	1 (2.0)	
Nausea and vomiting	0 (0)	5 (10.0)	
Intestinal paresis	1 (2.0)	2 (4.0)	
Urinary retention	0 (0)	1 (2.0)	0.281*
Clavien-Dindo grades of complications			
0	45 (90.0)	40 (80.0)	
I	2 (4.0)	6 (12.0)	
II	2 (4.0)	3 (6.0)	
IIIA	1 (2.0)	1 (2.0)	0.476*

* Chi-squared test.

In our study, amino acids, lidocaine, and magnesium showed an anti-inflammatory and analgesic effect in the first 5 PODs (the postoperative period examined in the study), as well as having a prokinetic effect. It seems that the synergism of these substances results in a prolonged beneficiary effect on postoperative inflammation and pain. Furthermore, it seems that this combination is useful in abdominal surgery. The choice to analyze the first 5 PODs was made in order to encompass the peak of the most commonly used postoperative inflammatory parameters, as well as the beginning of their return to baseline. Based on the literature search, we think that this is the first study to examine the effect of simultaneous use of these 3 substances in abdominal surgery.

This study has several limitations, which can be overcome with additional research. We did not analyze the isolated effects of lidocaine, magnesium, and amino acids – all patients in Group 1 received all the substances. Also, the sample was too small for advanced statistics. Future studies should be performed on larger samples including other surgical specialties and laparoscopic surgery, with the comparison of the effects of these individual substances.

Conclusions

In this paper, we showed the anti-inflammatory effect of simultaneous lidocaine, magnesium, and amino acids perioperatively use in abdominal surgery, as well as their beneficial effect on postoperative pain and peristalsis. Postoperative inflammation triggers pain through multiple mechanisms. Therefore, these results suggest that a reduction in inflammation consequently reduces postoperative pain. This study has certain implications for clinical practice and future research on multimodal analgesia and anti-inflammatory perioperative therapy.

Statement

The work was done at the Center for Digestive Surgery, Surgical Clinic of the Clinical Center of Montenegro.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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CRNA GORA - UNIVERZITET CRNE GORE
MEDICINSKI FAKULTET
UCG
Broj 31/1
Podgorica, 15.02. 2023 god.

Na osnovu člana 9 i stava 3 člana 31 a Pravila doktorskih studija (Bilten Univerziteta Crne Gore broj:513/20 i 561/22), a nakon razmatranja Drugog godišnjeg izvještaja mentora akademika prof. dr Ranka Lazovića i komentora prof. dr Ivana Palibrka o napredovanju doktoranda dr med Ognjenke Šarenac broj:31 od 10.01.2023.godine, Komisija za doktorske studije na sjednici održanoj dana 15.02.2023. godine je donijela

O D L U K U

1. Predlaže se Vijeću Medicinskog fakulteta da usvoji Drugi godišnji izvještaj mentora akademika prof. dr Ranka Lazovića i komentora prof. dr Ivana Palibrka o napredovanju doktoranda dr med Ognjenke Šarenac broj: 31 od 10.01.2023. godine.

2. Prijedlog komisije i Izvještaj mentora i komentora sa objavljenim radom iz tačke jedan ove Odluke, dostavljaju se Vijeću Medicinskog fakulteta, na dalje izjašnjenje.

Obrazloženje

U skladu sa stavom 1 člana 31a Pravila doktorskih studija, mentor akademik prof. dr Ranko Lazović i komentor prof. dr Ivan Palibrk, blagovremeno su dostavili izvještaj o napredovanju doktoranda dr med Ognjenke Šarenac, broj 31 od 10.01.2023. godine.

Na osnovu stava 3 člana 31 a Pravila doktorskih studija, Komisija za doktorske studije na sjednici održanoj dana 15.02.2023. godine, nakon razmatranja navedenog izvještaja mentora i komentora, konstatovala da izvještaj sadrži sve elemente, da je pravilno popunjen i na osnovu njega se stiče konkretan uvid o ostvarenom napretku kandidatkinje. Mentor i komentor su visokim ocjenama okarakterisali dosadašnji istraživački rad doktorantkinje i dostavili objavljeni rad kao rezultat doktorskih istraživanja. Priloženi podaci u IM obrascu ukazuju na posvećenost kandidatkinje.

Na osnovu navedenog Komisija je odlučila kao u dispozitivu ove Odluke.

DOSTAVLJENO
-Vijeću Medicinskog fakulteta
-Studentskoj službi

KOMISIJA ZA DOKTORSKE STUDIJE
PREDSJEDNIK

Prof. dr Filip Vukmirović