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INFLUENCE OF THE POSTOPERATIVE ANALGESIATACTICS ON THE DYNAMICS OF INTRA-ABDOMINAL AND ABDOMINAL PERFUSION PRESSURE IN PATIENTS WITH ACUTE SURGICAL PATHOLOGY OF THE ABDOMINAL CAVITY.

Structured abstract. Introduction: Intra-abdominal hypertension syndrome and abdominal compartment syndrome complicate the course of many surgical diseases of the abdominal cavity and lead to the development and progression of multiple organ failure. Determination of abdominal perfusion pressure and its dynamics allows to predict the development of multiple organ failure and adjust therapeutic tactics timely. The *aim* of the research study was to determine the impact of postoperative analgesia on the dynamics of intra-abdominal pressure and abdominal perfusion pressure in patients with intra-abdominal hypertension syndrome.

Methods: 82 patients with acute surgical pathology of the abdominal cavity and signs of intra-abdominal hypertension were examined. All patients were divided into three groups according to the chosen method of postoperative analgesia: group 1 (n = 30) - opioid analgesia, group 2 (n = 30) - continued intravenous infusion of 1% lidocaine solution in combination with the administration of ketorolac 30 mg three times a day, group 3 (n = 22) - epidural analgesia using 1% lidocaine solution. Intra-abdominal pressure in the bladder was measured in all patients every 6 hours according to the standard method and the calculation of abdominal perfusion pressure. The patient groups were comparable in age, sex, and severity.

Findings: The research study found that no relevant difference in the studied indices of abdominal perfusion pressure when using different types of analgesia was noted, instead, the best profile at the level of intra-abdominal pressure was of epidural analgesia.

Conclusions: use of epidural analgesia significantly reduces intra-abdominal pressure over time.The impact of various methods of analgesia in the postoperative period in acute surgical pathology of the abdominal cavity does not differ in the effect on the abdominal perfusion pressure.

Keywords: intra-abdominal hypertension, abdominal compartment syndrome, abdominal perfusion pressure

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Abbreviations: IAP - intra-abdominal pressure, APP - abdominal perfusion pressure.

Introduction. The development of multiple organ failure is a leading cause of death in patients with acute surgical pathology. An important role in this is played by the abdominal compartment syndrome, the mortality rate in which, without treatment, is close to 100%. Increase in intra-abdominal pressure above 10 mm Hg during 1-2 days leads to death in 3 - 7% of cases. And when this value is more than 35 mm Hg within 6-7 hours then such increasing results in 100% fatality. The abdominal compartment syndrome is currently defined as a sustained increase in intra-abdominal pressure to a level greater than 20 mm Hg, which is associated with onset of organ failure/dysfunction. Also important is the fact that, unlike the phenomenon of intra-abdominal hypertension, the abdominal compartment syndrome does not require classification by the level of intra-abdominal hypertension, since this syndrome in modern literature is represented by the phenomenon of "all or nothing" (meaning that further increase of intra-abdominal pressure is of no importance in the developing abdominal compartment syndrome at any degree of intra-abdominal hypertension) [1, 2, 3].Chad G. Ball [3] et al. indicate that coagulopathy with thrombocytopenia less than 55,000 per μl, an increase in APTT beyond twice the upper normal limit, prothrombin time more than 1.5 seconds, MHC over 1,5, sepsis, intra-abdominal infections, PS/PEEP, large body mass index (above 30 kg/m2), laparoscopic interventions, position of the patient in prone position, damage control surgery, acute pancreatitis are risk

factors for abdominal compartment syndrome[4].William K R and Luis Garsia [5] point to acidosis with a pH less than 7.2, hypothermia with a core temperature below 34 degrees, blood loss more than 4000 ml, the need for transfusion of more than 10 units of blood, systolic blood pressure below 70 mmHg, lactate level more than 5 mmol/L, base deficit greater than 6 in patients older than 55 years and - 15 in patients younger than 55 years. Bladder pressure measurement is a simple and reliable method. It is important to measure the perfusion pressure of the abdominal cavity, which determines the severity and prognosis of intra-abdominal hypertension syndrome. It constitutes the difference between the average blood pressure and intra-abdominal pressure. The level of perfusion pressure below 60 mm Hg is associated with patient survival. *The aim of the research study* was to determine the impact of postoperative analgesia tactics on the dynamics of intra-abdominal pressure and abdominal perfusion pressure in patients with intra-abdominal hypertension syndrome.

Methods. 82 patients with acute surgical pathology of the abdominal cavity and signs of intra-abdominal hypertension were examined. All patients were divided into three groups according to the chosen method of postoperative analgesia: group 1 (n = 30) - opioid analgesia, group 2 (n = 30) - continuous intravenous infusion of 1% lidocaine solution in combination with administration of ketorolac 30 mg three times a day, group 3 (n = 22) - epidural analgesia using bolus injection of 1% lidocaine solution. Inclusion criteria. All patients 18 to 80 years of age were included, in whom acute surgical pathology of the abdominal cavity developed within 24 hours before hospital admission. They had not severe concomitant chronic diseases or decompensated diseases. All patients had surgery on the first day of hospital admission. Exclusion criteria were age discrepancy (younger than 18 and older than 80 years old), a disease lasting more than 24 hours, delay in surgery on the first day of hospital admission, and comorbid chronic conditions at the decompensation stage. The patients who died within 72 hours of observation were excluded. The structure of the surgical pathology was as follows: peritonitis - 15 patients (survived - 9, died - 6), destructive pancreatitis - 19 patients (survived - 12, died - 7), intestinal obstruction - 9 patients (survived - 7, died - 2), obstructive jaundice - 4 (all patients survived), gastrointestinal bleeding - 5 (survived - 4, died - 1), polytrauma with hemoperitoneum and abdominal trauma - 13 patients (survived - 12, died - 1), mesenteric thrombosis - 3 (survived - 1, died - 2), destructive cholecystitis - 4 (survived - 2, died - 2), sigmoid perforation associated with malignant tumor - 2 (survived - 2), tumor-associated hemoperitoneum- 1 (died - 1), multiple infected pancreatic cysts with perforation - 2 (died - 2), duodenal perforation - 2 (survived - 1, died - 1), bilateral tubo-ovarian abscesses with perforation - 2 (survived - 2). Of 82 patients survived 57 patients (69.51%) and 25 (30.49%) patients died after ending of the observation period. The observation period lasted 72 hours. The surgical procedures were performed in all patients under total intravenous multimodal anesthesia with tracheal intubation and mechanical ventilation. In the postoperative period, opioid analgesia was performed by the scheduled administration of opioid analgesics (morphine hydrochloride, promedol) at regular time intervals. Intravenous continuous infusion of 1% lidocaine solution was initiated at the end of surgery. Bolus doze of 1.5 mg/kg of 1% lidocaine was intravenously administered within 20 minutes. In the time following the infusion was carried out within 24 hours at a rate of 1 mg/kg/h. Epidural analgesia was performed after the catheter was inserted into the epidural space according to the standard technique at the level of Th X using bolus injection of 6 ml of 1% lidocaine solution at regular time intervals. The epidural catheter was inserted immediately after the patient's return from operating room. Hypotension and development of neurotoxicity were not observed. Intra-abdominal pressure was measured by the standard method in the bladder every 6 hours. After each IAP measurement, abdominal perfusion pressure was calculated. Informed consent was obtained from each patient. This research study is a part of the scientific work of the Department of Surgery with the course of dentistry of Vinnytsia State Medical University named after M.I. Pirogov. The research study was approved by the Ethics Committee in November 2017. The demographic data are presented in Table 1. All patients were the representatives of European race. As the analytical frame of the research study, the profile analysis developed in 2001 by US statisticians (Barbara G. Tabachnik & Linda S. Fidell, 2001) was used as a modification of multivariate covariance analysis and repeated measures. We used Ras an analytical platform for calculations. Namely, we used Anova function from the ***car*** library [6, 7].

Table 1.

Gender division by analgesia groups.

Gender	Opioids n = 30		Lidocaine n = 30		Peridural analgesia n = 20	
	survived	died	survived	died	survived	died
Male	15	5	14	6	9	1
Female	6	4	8	2	6	6

Results. The main objective was to investigate the significant differences in the clinical efficacy of different anesthesia regimens for surgical procedures. The efficacy of analgesia has been studied according to the dynamics of intra-abdominal and abdominal perfusion pressures measured at the beginning and at regular 6-hour time intervals by 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72 hours (total 13 time points). The analysis included a study of the **level effects,** that is, a comparison of the time-integrated clinical effects of the compared analgesic regimens. The traditional methodology of clinical trials of drugs is based on the effects of levels. However, in real cohorts of patients in clinical practice, the situation is different. An important difference is that different regimens are used for different values of clinical parameters. This leads to a shift in the assessment of the clinical efficacy of the analgesic regimens by the level effects as shown below. Therefore, we have included an analysis of the **effects of dynamics** and the **effects of concurrency,** given the panel nature of data organization. Dynamic analysis indicates that the effect of the dynamics of clinical characteristics is independent of the treatment regimen and other confounding factors. Separating out the effect of the dynamics is extremely important. If the effect is insignificant, we can say about absence of clinical effect of the comparable anesthesia regimens as a whole. *The effects of concurrency are testimony to the peculiarities of the dynamics of clinical characteristics in different anesthesia regimens and are fundamental to assert the significance of differences in the clinical efficacy of the anesthetics compared.* To control findings bias due to the presence of confounding effects of other influential factors, we included the patient's age and gender as covariates. Considering their important impact on the choice of anesthesia type and the anesthesia efficacy, we separated the confounding effect of these characteristics by analyzing their partial effects and provided data in the tables of analysis results. To illustrate the meaningful interpretation of the differences in the effects of the compared analgesic regimens, the direction of the dynamics of efficacy indicators, we present the group mean of intra-abdominal and abdominal perfusion pressures in the dynamics cleared off confounding effects of the aforementioned covariates. For the purpose of the research analytical frame, we used the profile analysis developed in 2001 by US statisticians (Barbara G. Tabachnik & Linda S. Fidell, 2001) as a modification of multivariate covariance analysis with repeated measurements. We used the platform ***Ras*** analytical calculations. Namely, we used *Anova* function from the ***car*** library [8, 9]. Due to the imbalance of the design (30x30x22 according to the type of anesthesia), the effects and sums of boxes according to Schedule II were previously obtained on the basis of ***lm*** function of R ***stats*** statistic library [6, 7].

The direct test is multidimensional Repeated Measures MANOVA Pillai test [8, 9]. Polynomial contrasts were used to reproduce the effects of the dynamics. We used *contr. Poly* function of R ***stats*** statistic library to find the matrix of contrasts. The results of the profile analysis of intra-abdominal pressure dynamic are shown in Table 2, graphical representation in Fig. 1 Type 1 (red) - opioids, type 2 (blue) - lidocaine, type 3 (green) - epidural analgesia.

Table 2.

The results of the profile analysis of the intra-abdominal pressure dynamics (Type II Repeated Measures MANOVA Tests: Pillai test statistic)

Effects of levels	Df	*Pillai	F	Df1	Df2	p	
(Intercept)	1	0.54563	93.666	1	78	5.256e-15	***
Treatment	1	0.06449	5.377	1	78	0.02303	*
Gender	1	0.00132	0.103	1	78	0.74929	
Age	1	0.00077	0.060	1	78	0.80695	
IAP	1	0.54186	6.604	12	67	1.254e-07	***
Concurrency							
Treatment: IAP	1	0.18627	1.278	12	67	0.25216	
Gender: IAP	1	0.14740	0.965	12	67	0.49012	
Age: IAP	1	0.09536	0.589	12	67	0.84386	

Dynamic							
IAP	1	0.53315	6.662	12	70	8.479e-08	***

Note* Df – degrees of freedom in Pillai test; Df1 and Df2 – degrees of freedom in F test

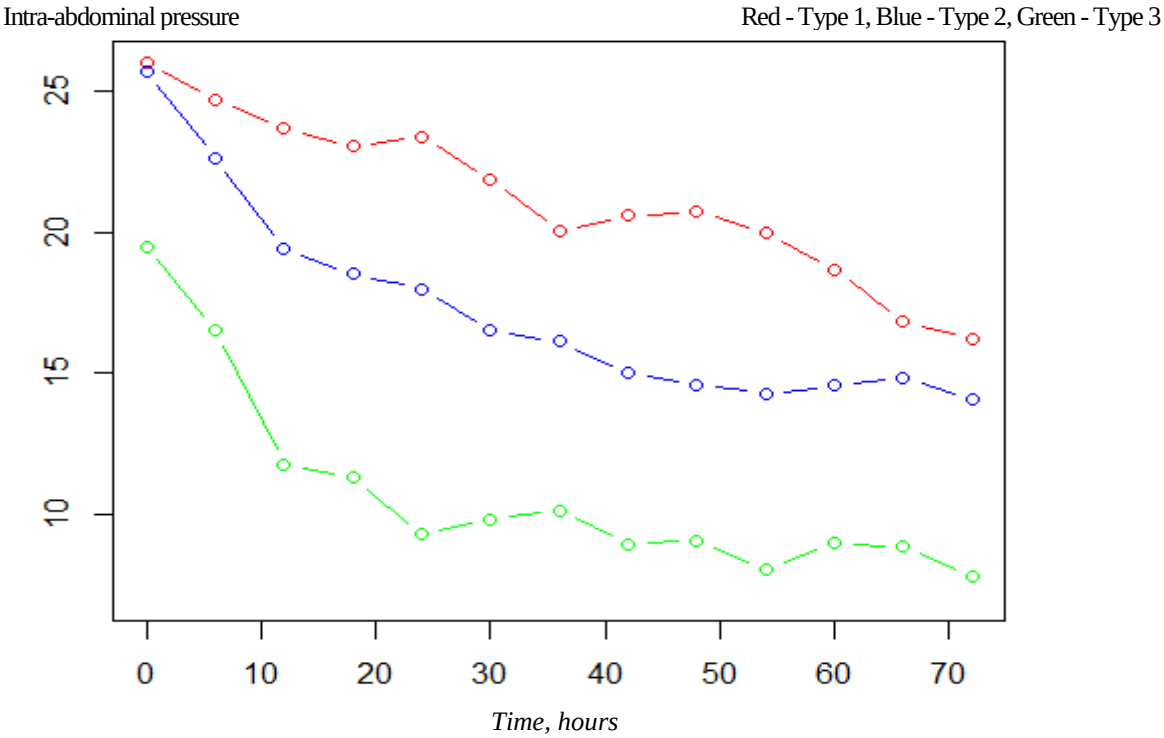

Fig.1. Profiles of the mean value dynamics of intra-abdominal pressure according to different types of anesthesia

Level effects. Table 1 and Fig. 1 imply that intra-abdominal pressure levels were reliably (p = 0.02303) the highest for analgesia type 1 and the lowest for analgesia type 3. Gender and age did not significantly affect the mean levels of the profiles, the corresponding p-levels were 0.74929 and 0.80695. In general, individual levels of intra-abdominal pressure of the patients (IAP effect) were significantly different from each other (p=1.254e-07). The effects of concurrency by the anesthesia type (Treatment: IAP), age (Age: IAP) and gender (Gender: IAP) were unreliable, corresponding p-levels were 0.25216, 0.84386 and 0.49012.In other words, the rates of increase in intra-abdominal pressure were not significantly different according to the anesthesia types.The effect of dynamic is highly reliable (p=8.479e-08), that means levels of intra-abdominal pressure were reducing significantly within the observation period. The results of the profile analysis of the abdominal perfusion pressure dynamic are specified in Table 3, graphic representation at Fig. 2 Type 1 (red) – opioids, type 2 (blue) – lidocaine, type 3 (green) – epidural analgesia.

Table 3.

The results of the profile analysis of the abdominal perfusion pressure dynamic (Type II Repeated Measures MANOVA Tests: Pillai test statistic)

Effects of levels	Df	Pillai	F	Df1	Df2	p	
(Intercept)	1	0.94436	1323.86	1	78	<2.2e-16	***
Treatment	1	0.02608	2.09	1	78	0.1524	
Gender	1	0.00051	0.04	1	78	0.8422	
Age	1	0.01987	1.58	1	78	0.2124	
APP	1	0.48355	5.23	12	67	4.068e-06	***
Concurrency							
Treatment: APP	1	0.09246	0.57	12	67	0.8594	
Gender: APP	1	0.12219	0.78	12	67	0.6714	
Age: APP	1	0.12995	0.83	12	67	0.6157	
Dynamic							
APP	1	0.47586	5.3	12	70	2.855e-06	***

Level effects. Table 3 and Fig. 2 imply that levels of abdominal perfusion pressure were not reliably different according to the anesthesia types (p=0.1524). Gender and age did not significantly affect the mean levels of the profiles, the corresponding p-levels were 0.8422 and 0.2124. In general, individual levels of abdominal perfusion pressure of the patients (APP effect) were significantly different from each other (p=4.068e-06).

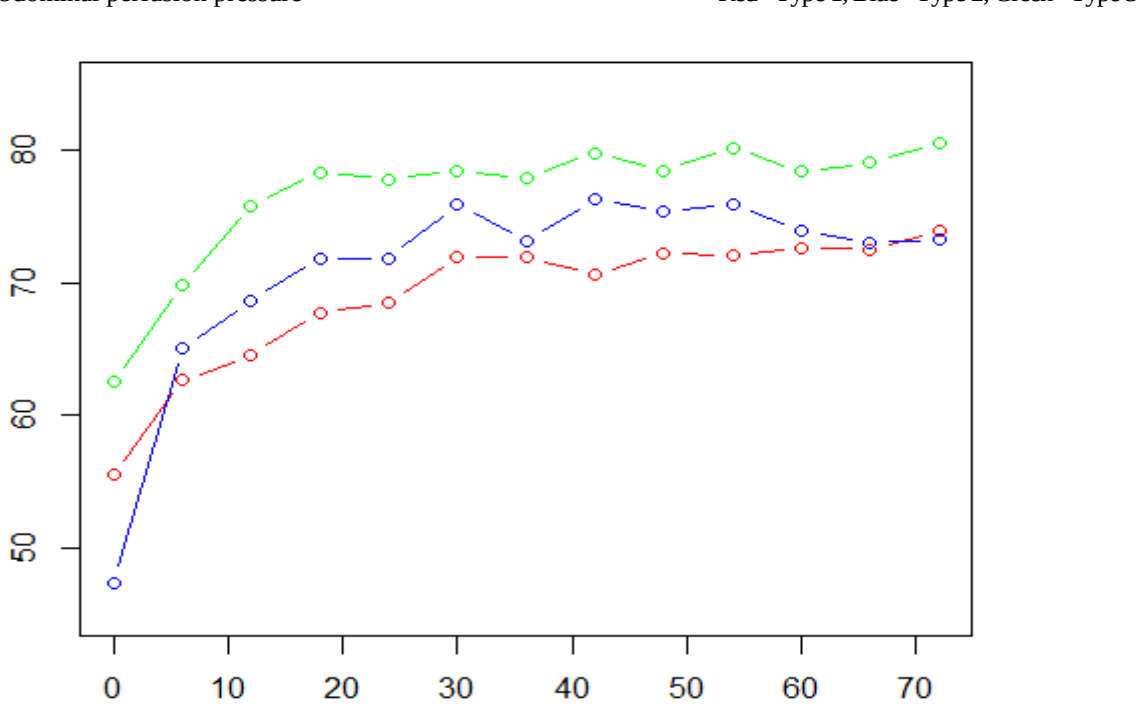

Fig. Profiles of the mean value dynamics of abdominal perfusion pressure according to different types of anesthesia

The effects of *concurrency* by the anesthesia type (Treatment: APP), age (Age: APP), and gender (Gender: APP) were unreliable, corresponding p-levels were 0.8594, 0.6157, 0.6714. That is, the rates of increase in abdominal perfusion pressure were not significantly different according to the anesthesia types. The effect of the *dynamic is* highly reliable (p = 2.855e-06), that means the levels of abdominal perfusion pressure were increasing significantly during the observation period.

Discussion. The results obtained to some extent correspond to the results reported in other research studies, which, in particular, indicate the advantages of the continuous epidural analgesia use. The use of such analgesia reduces pain syndrome, optimizes the work of breathing and adaptation of the patient to the artificial pulmonary ventilation, relieves coughs and stimulates peristalsis [10, 12]. The epidural analgesia decreases the concentration of proinflammatory cytokines in the blood and eliminates the onset of the systemic inflammatory response syndrome [11, 13], decreases the risk of metastasis in cancer patients having surgery. Improvement in pancreatic perfusion when used with epidural anesthesia is indicated by M. Sadowski et al. [14, 15] that is confirmed by A. Demirag et al. according to whom the use of epidural anesthesia restores pancreatic microcirculation and decreases the severity of acute pancreatitis. Thoracic epidural anesthesia/analgesia is "golden standard" for the treatment of pain syndrome in this pathology [15] and has advantages over the use of tramadol and opioids [16]. Epidural anesthesia/analgesia reduces postoperative pulmonary complications, increases intestinal blood flow, and reduces onset of acidosis of epithelial cells, which is also associated with the increased perfusion pressure. The similar view is expressed by Windish O. [17] regarding the use of thoracic epidural analgesia. The review 2016 points that thoracic epidural analgesia causes splanchnic vasodilation, improves intestinal mucosal perfusion, and increases intramucosal pH in patients with peritonitis. The epidural block at T2-T10 levels improves circulatory dynamics and global oxygen delivery, and carrying out thoracic epidural anesthesia only in 8% of patients was associated with hypotension, which was well adjusted by sympathomimetic agents, and catheter dislocation was indicated in 17 - 24% of cases. In the same review, there are indications that the animal models (rats) proved the reduction of bacterial translocation episodes, liver failure, and improvement of intestinal wall perfusion. The review 2017 published by Bulyez et al. [17, 27] analyzing intensive treatment of acute pancreatitis once again stated that the advantages of epidural anesthesia/analgesia in this pathology are the increase in the intestinal barrier function, splanchnic, pancreatic and renal perfusion,

reduction of the liver damage and inflammatory response as well as mortality reduction (EPIPAN research study). Epidural analgesia is an integral part of ERAS protocols for patient management after colorectal laparoscopic surgery [16, 27]. Information on the use of continuous lidocaine infusion in patients with intra-abdominal hypertension syndrome have not been found. Lidocaine is an amide local anesthetic that has analgesic, anti-hyperalgesic and anti-inflammatory properties [18, 19]. Intravascular use of lidocaine is described for obliterating diseases of the vessels of the lower extremities [20]. Analgesic effects are thought to be mediated by the suppression of spontaneous impulses generated from injured nerve fibers due to the blockade of sodium channels, potassium channels, muscarinic and dopamine receptors [21]. Also local anesthetics, in particular lidocaine, are characterized by antiarrhythmic (blockade of the sodium channels of the cardiac conduction system), antithrombotic (inhibition of platelet aggregation due to limitation of calcium entry into the cell), anti-inflammatory effect due to inhibition of migration and degranulation of leukocytes that is due to the blockade of neuronal transmission, as well as the effect of preventing central sensitization (as there is no release of cytokines and inflammatory response at the tissue level), antibacterial and neuroprotective effects [22].If bupivacaine and ropivacaineare characterized by a decrease in clearance associated with the patient's age, lidocaine has no similar properties and can be used in the group of elderly people [23]. The advantages of using lidocaine are low cost, efficacy in abdominal surgery, reduced opioid use, ileus minimization, reducing length of stay in hospital, reducing nausea and vomiting, and postoperative pain. Recommended lidocaine regimens are associated with low drug toxicity and are 1.5 mg/kg bolus within 20 minutes with next infusion of 1.5 mg/kg/hour during one to three days. For example, Koppert et al. showed a reduction in postoperative pain and morphine use in patients having extensive abdominal surgery with continuous lidocaine infusion, although the research has its limitations, since the represented group of patients are the patients having received surgical treatment for colorectal diseases. However, experts of the Cochrane Collaboration, on the contrary, point to the lack of data regarding the positive effects of continuous lidocaine infusion [21]. The review 2017inBritish Journal of Pain indicates the safety of using continuous lidocaine infusion at high doses in the absence of liver failure, as 90% of lidocaine is metabolized by the cytochrome P450. The effect of systemic infusion of lidocaine is seen even with a decrease in its plasma concentration. Intravenous lidocaine administration reduces opioids use by 10 - 12 times and production of proinflammatory cytokines [18] and can be used in the treatment of postoperative pain. The efficacy of the method in the first 24 hours of the postoperative period was proved by Weibel S et al (2018) [21]. The efficacy of perioperative infusion for the prevention of chronic post-surgical pain has been shown in the work by Bailet M et al.(2018), Dewinter Get al. (2018) [23]. Although there are no data on the use of continuous lidocaine infusion in patients with intra-abdominal hypertension - abdominal compartment syndrome, given the above, the method can be considered pathogenetically sound. Ketorolac tromethamine is a non-steroidal anti-inflammatory drug with potent analgesic and moderate anti-inflammatory effect. The first reports on the properties of the drug were received in the 1990s of the XX century, where its use was considered as a supplement to opioid analgesia. In review 2000, the efficacy of a single dose of ketorolac in the early postoperative period was positively evaluated by Smith et al. [24]. After intramuscular injection, the maximum concentration of the drug in the plasma is determined after 45 - 60 minutes. The drug binds well to albumin and has a lower clearance than narcotic analgesics. The analgesic effect of ketorolac is related to the racemic concentration of S- and R-forms of the drug, and in the case of i.m. administration, a lower clearance of the S-enantiomer is possible compared to intravenous administration, which can lead to better analgesic effect. There are also nasal forms of the drug in the form of a spray [25]. Ketorolac is metabolized principally by glucuronic acid conjugation. Also a small amount of the drug is metabolized by means of hydroxylation and p-hydroxyketorolac formation, which has little analgesic activity. Clearance is significantly reduced in patients over 65 years of age. According to the data of Alan D. Kaye et al., an alternative to high doses of opioids is the use of ketorolac in combination with regional blockades. The use of the drug in various fields of surgery, traumatology, in particular after knee prosthetics, abdominal hysterectomy, where the drug showed advantages over diclofenac and acetaminophen and showed no significant side effects, is considered sound [23]. The drug side effects are prolonged bleeding time, but without clinically significant effect, inhibition of platelet aggregation, a slight increase in creatinine levels in elderly patients, which is transient. Particularly common occurrence of side effects is possible in patients over 65 years of age with concomitant hypovolemia, cirrhosis, use of vasoactive drugs. The development of kidney failure has not been reported in any research study. At a dose of 60 mg/day, the drug effectively prevented the development of postoperative nausea and vomiting [26]. J.B. Foresteret al. reported the possibility of developing bronchospasm when using ketorolac in patients with aspirin intolerance. A.Ye. Karatieiev points out that the incidence of renal dysfunction when using ketorolac did not differ from that in diclofenac and paracetamol. The recommended daily dose of ketorolac is 90 mg, single dose of 30 mg. Routes of administration are intravenous, intramuscular, intranasal (spray) [24, 26].

Conclusion. Thus, as a result of the research carried out, significant advantages of epidural analgesia impact on the dynamics of intra-abdominal pressure were established. There were no significant differences in the studied indices of abdominal perfusion pressure when using opioid analgesia, continuous intravenous 1% lidocaine infusion and epidural analgesia. Adverse

effects of continuous intravenous infusion of 1% lidocaine solution were not noted. Similarly, no manifestations of neurotoxicity and hypotension were observed during bolus injection of 1% lidocaine into the epidural space. Comparative studies are needed as to continuous epidural administration of this local anesthetic and other local anesthetics, including bupivacaine and ropivacaine.

Conflict of interest: the authors declare no conflict of interest.

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