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CLINICAL AND LABORATORY CHANGES IN POSTSURGICAL PAIN MARKERS IN CHILDREN

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Summary

Postoperative pain in children remains a significant problem in pediatric intensive care, possibly related to an imperfect algorithm for its management. Prolonged postoperative pain delays recovery and rehabilitation, increases treatment costs, and prolongs opioid use. Inadequate perioperative pain management can lead to a variety of postoperative complications, the prediction of which remains elusive despite the use of commonly accepted clinical, laboratory, and instrumental indicators.

The aim *of this study was to evaluate clinical and laboratory changes in children after abdominal surgery and their correlation with acute pain scales.*

Material and Methods. *The study included 83 children aged 7-18 years who underwent abdominal surgery under opioid anesthesia.*

Inclusion criteria: age 7-18 years; indication for surgery for acute appendicitis; American Society of Anesthesiologists (ASA) Anesthesia Risk Score I and II; parental consent for the children to participate in the study.

Acute pain intensity was measured using the Visual Analog Scale (VAS) and the Face, Legs, Activity, Cry, Consolability (FLACC) scale. Key vital signs assessed included heart rate, respiratory rate, systolic and diastolic blood pressure, and oxygen saturation (SpO2). In addition, laboratory indicators including leukocyte count, blood glucose level, erythrocyte sedimentation rate, and TLR-4 and CD40L levels were determined.

All clinical and laboratory studies were conducted in accordance with the World Medical Association Declaration of Helsinki «Ethical Principles for Medical Research Involving Human Subjects» (Minutes of the Ethics Committee No. 2, dated February 24, 2002).

Statistical analysis was performed on a personal computer using Statistica 10 software, using parametric and nonparametric statistical methods.

The study is a part of the research project of the Department of Children's Diseases of the Postgraduate Medical Education Faculty of the Ivano-Frankivsk National Medical University «Health Status and Adaptation of Children from the Precarpathian Region with Somatic Diseases, Their Prevention» 2021-2026, state registration number 0121U111129; the author is a co-researcher.

Results. *The mean age of the children was 13.8±0.23 years, while the mean body weight was 40.9±1.6 kg. Gender assessment showed no differences between boys and girls (55.4 % and 44.6 %, respectively, p>0.05).*

The study showed very strong positive correlations (r=0.9-1.0) between acute pain assessment scores on the VAS and FLACC scale and heart rate, blood glucose levels; strong positive correlations (r=0.7-0. 9) with total leukocyte count and erythrocyte sedimentation rate; moderate positive correlations (r=0.5-0.7) with serum TLR4 and CD40L levels; weak positive correlations (r<0.5) with diastolic blood pressure, SpO2, and opioid and non-opioid analgesic administration.

Conclusions. *The observed positive correlations between acute pain scores on the VAS and FLACC scale and pro-inflammatory indicators may support the theory of involvement of these markers in the generation of acute pain in pediatric patients. However, further research is needed to investigate the mechanisms of acute postoperative pain generation, to identify markers related to nociception in chronic pain, and to develop preventive strategies for these conditions in children.*

Key words: *children; acute postoperative pain; CD40L system; TLR4; FLACC scale; Visual Analog Scale.*

Introduction

Postoperative pain in children remains a significant problem in pediatric intensive care, possibly related to an imperfect algorithm for its management. Prolonged postoperative pain delays recovery and rehabilitation, increases treatment costs, and prolongs opioid use [1-3]. Inadequate perioperative pain management can lead to a variety of postoperative complications, the prediction of which remains elusive despite the use of commonly accepted clinical, laboratory, and instrumental indicators [4-7].

Toll-like receptor 4 (TLR4) expression may serve as a specific marker of acute postoperative pain. According to the literature, opioid exposure induces neuroinflammatory responses via glial TLR4 expression [8]. TLR4 stimulation leads to overproduction of pro-inflammatory mediators underlying inflammatory and autoimmune diseases, including sepsis, neuropathic pain and neurodegenerative diseases [9]. To date, opioid agonists have been shown to act as TLR4 agonists, while opioid antagonists such as naloxone act as TLR4 antagonists [10]. In addition, opioids can induce paradoxical hyperalgesia, a phenomenon that is directly dependent on the baseline level of TLR4 [11]. The results of recent studies also indicate the impact of TLR4 stimulation on the induction, conversion and modulation of chronic pain [12]. There is evidence that opioids, including morphine, can induce neuroinflammatory responses, in part mediated via glial TLR4 expression [13-15]. The interaction of TLRs in response to opioids results in paradoxical hyperalgesia, a state of increased pain sensitization induced by opioid exposure [16].

Experimental models of peripheral nerve injury have shown that the CD40/CD40 ligand (CD40L) system plays an important role in the generation of neuropathic pain associated with increased chemokine (CCL2) and calcitonin gene-related peptide (CGRP) expression [17-23]. However, the available literature on the pronociceptive effects of the CD40-CD40L system in the experiment is quite limited, and its role in the development of pain syndrome in clinical medicine, especially in anesthesia practice, remains unstudied.

The aim of this study was to evaluate clinical and laboratory changes in children after abdominal surgery and their correlation with acute pain assessment scales.

Material and Methods. The study included 83 children aged 7-18 years who underwent abdominal surgery under opioid anesthesia in the surgical department of the municipal non-profit enterprise «Ivano-Frankivsk Regional Children's Clinical Hospital of the Ivano-Frankivsk Regional Council», Ivano-Frankivsk, Ukraine, in 2020-2022.

Inclusion criteria were as follows: age 7-18 years; indication for surgery for acute appendicitis; American Society of Anesthesiologists (ASA) anesthesia risk score of I and II; parental consent for children's participation in the research.

Exclusion criteria included children under 7 years of age; ASA anesthesia risk score of III and higher; mental disorders; neoplasms or tumors; previous abdominal surgery; chronic pain for six months prior to surgery; parent/guardian refusal to enroll their children in the research.

Acute pain intensity was measured using the Visual Analog Scale (VAS) [24] and the Face, Legs, Activity, Cry, Consolability (FLACC) scale [25]. The VAS and FLACC scale scores were obtained on days 1, 3, and 6 after surgery.

During the first six days after surgery, the children's vital signs, including heart rate (HR), respiratory rate (RR), systolic and diastolic blood pressure (SBP, DBP), and oxygen saturation (SpO2), were monitored. In addition, laboratory indicators including leukocyte count, blood glucose level, and erythrocyte sedimentation rate (ESR) were determined.

The level of TLR4 was measured in the blood of 48 patients using an enzyme-linked immunosorbent assay (ELISA) kit from Elabscience, lot TM5TMWVDI (USA), according to the manufacturer's instructions at hospital discharge, three months, and six months after surgery. The results obtained were determined by the absorbance of the studied samples on the microtiter plate reader «HumaReader» (Germany) at a wavelength of 450 nm. The minimum possible concentration of determination is 1 pg/ml.

Serum CD40L levels were measured in 30 patients using the Human CD40L (Cluster of Differentiation 40 Ligand) ELISA Kit, Catalog No: EH0086 (Fine Biotech, Wuhan, China) according to the manufacturer's instructions during surgery, 24 hours after surgery, and at hospital discharge.

All clinical and laboratory studies were conducted in accordance with the World Medical Association Declaration of Helsinki «Ethical Principles for Medical Research Involving Human Subjects». In accordance with the law, a written informed consent was signed by each subject (parents/guardians) prior to participation in the study. The manuscript was approved by the Ethics Committee of the Municipal Non-Profit Enterprise «Ivano-Frankivsk Regional Children's Clinical Hospital of the Ivano-Frankivsk Regional Council», as evidenced by the extract from the Minutes of the Committee Meeting No. 2 dated February 24, 2002.

Statistical analysis was performed on a personal computer using the statistical software packages MS Excel and SPSS22 for Windows. If the data were normally distributed (Shapiro-Wilk test >0.05), parametric statistical methods were used, calculating the arithmetic mean (M) and the standard error of the mean (m). The dependent samples t-test was used to compare quantitative indicators with a normal distribution. The relationship between indicators was determined using Pearson's correlation coefficient. The difference between parameters was considered statistically significant at $p<0.05$.

If the data followed a non-normal distribution (Shapiro-Wilk test <0.05), non-parametric statistical methods were used, calculating the median (Me), lower quartile (LQ) and upper quartile (UQ). The Wilcoxon signed-rank test was used to assess differences between nonparametric indicators. The relationship between indicators was determined using Spearman's correlation. Parameter differences were considered statistically significant at $p<0.05$.

The study is a part of the research project of the Department of Children's Diseases of the Postgraduate Medical Education Faculty of Ivano-Frankivsk National Medical University «Health Status and Adaptation of Children from the Precarpathian Region with Somatic Diseases, Their Prevention» 2021-2026, state registration number 0121U111129; the author is a co-researcher.

Results and Discussion. The mean age of the children was 13.8±0.23 years, while the mean body weight was 40.9±1.6 kg. Gender assessment showed no differences between boys and girls (55.4 % and 44.6 %, respectively, $p>0.05$).

Analysis of acute pain assessment in children using the VAS and FLACC scale showed a decrease in pain intensity during the first six days after surgery (Table 1).

No statistically significant difference was found in the main vital signs (RR, SBP, DBP, and SpO2) over the course of treatment. However, a statistically significant decrease in HR was observed on the sixth day after surgery compared to the first day (Table 2).

Table 1

Acute pain assessment on the VAS and FLACC scale (n=83, M±m)

Day after surgery	VAS (points)	FLACC (points)
1	6.81±0.09	6.69±0.11
2	5.87±0.1	5.87±0.12
3	5.04±0.11	5.07±0.12
4	4.06±0.14	4.25±0.13
5	3.34±0.11	3.49±0.13
6	2.51±0.14	2.77±0.13
Dependent samples t-test	P_{1-4}=0.038 P_{1-5}=0.01 P_{1-6}=0.005 P_{2-6}=0.027	P_{1-5}=0.017 P_{1-6}=0.008 P_{2-6}=0.038

Table 2

Changes in patients' vital signs over the course of treatment (n=83, M±m)

Indicator	Day after surgery	Indicator value	Dependent samples t-test
HR, bpm	Day 1	96.15±1.64	$P_{1:3}>0.05$ $P_{1:6}<0.001$ $P_{3:6}>0.05$
	Day 3	93.9±1.35	
	Day 6	87.79±1.06	
RR, bpm	Day 1	21.09±0.24	$P_{1:3}>0.05$ $P_{1:6}>0.05$ $P_{3:6}>0.05$
	Day 3	21.07±0.23	
	Day 6	20.67±0.17	
SBP, mm Hg	Day 1	108.64±1.13	$P_{1:3}>0.05$ $P_{1:6}>0.05$ $P_{3:6}>0.05$
	Day 3	108.79±0.93	
	Day 6	107.13±0.85	
DBP, mm Hg	Day 1	67.09±0.94	$P_{1:3}>0.05$ $P_{1:6}>0.05$ $P_{3:6}>0.05$
	Day 3	69.22±0.86	
	Day 6	68.14±1.01	
SpO_2, %	Day 1	97.77±0.07	$P_{1:3}>0.05$ $P_{1:6}>0.05$ $P_{3:6}>0.05$
	Day 3	97.83±0.08	
	Day 6	97.75±0.09	

Analysis of correlations between acute pain scores on the VAS and FLACC scale and vital signs in pediatric patients on days 1, 3, and 6 postoperatively is presented in Table 3.

Table 3

Correlation coefficients between acute pain assessment scores on the VAS and FLACC scale and vital signs in children, p<0.05

Indicator	Day after surgery	VAS	FLACC
RR, bpm	Day 1	0.95	0.95
	Day 3	0.96	0.96
	Day 6	0.97	0.98
DBP, mm Hg	Day 1	0.36	0.36
	Day 3	0.36	0.36
	Day 6	0.42	0.41
SpO_2, %	Day 1	0.39	0.39
	Day 3	0.36	0.36
	Day 6	0.38	0.39

Analysis of the mean total blood leukocyte count showed statistically significant differences in this indicator during the course of treatment, namely 16.79±0.51 g/L on day 1, 12.99±0.41 g/L on day 3, and 9.13±0.28 g/L on day 6 after surgery ($p_{1:3}<0.001$, $p_{1:6}<0.001$). The mean ESR was 8.04±0.32 mm/h, 9.79±0.41 mm/h, and 8.91±0.33 mm/h on days 1, 3, and 6 after surgery, respectively ($p_{1:3}=0.001$). The mean incidence of pathologically elevated ESR (>12 mm/h) in the children studied did not show statistically significant changes during the first six days after surgery (8.4 %, 8.4 %, and 12.0 % of cases on day 1, day 3, and day 6, respectively). Evaluation of blood glucose level in children also showed changes in this indicator during the course of treatment, namely 5.97±0.11 mmol/l on day 1, 5.57±0.08 mmol/l on day 3, and 4.99±0.04 mmol/l on day 6 after surgery ($p_{1:3}<0.001$, $p_{1:6}<0.001$, $p_{2:3}<0.001$).

Correlations between acute pain assessment scores on the VAS and FLACC scale and paraclinical indicators in patients on days 1, 3, and 6 postoperatively are shown in Table 4.

Table 4

Correlation coefficients between acute pain assessment scores on the VAS and FLACC scale and paraclinical indicators in children, p<0.05

Indicator	Day after surgery	VAS	FLACC
Total leukocyte count, g/L	Day 1	0.83	0.83
	Day 3	0.96	0.91
	Day 6	0.93	0.93
ESR, mm/h	Day 1	0.84	0.84
	Day 3	0.84	0.84
	Day 6	0.84	0.84
Glucose, mmol/l	Day 1	0.98	0.98
	Day 3	0.99	0.99
	Day 6	0.99	0.99

Perioperative pain management in children is often ineffective, with up to 50 % of patients experiencing inadequate pain control and severe side effects from opioid analgesics. According to the literature, an increase in opioid use increases the prevalence of chronic pain [24]. The study analyzed the frequency of opioid and non-opioid analgesic administration to children in the perioperative period. In the analgesic regimen, fentanyl was administered to 82 (98.8 %) children, promedol to 19 (22.9 %) children, omnopon to 5 (6.02 %) children, morphine to one (1.2 %) child, and ketamine to 29 (34.9 %) children. The following non-opioid analgesics were also used for pain relief Analgin in 63 (75.9 %) cases and acetaminophen in 57 (68.6 %) cases. On the first postoperative day, statistically significant positive correlations ($p<0.05$) were found between the acute pain score on the VAS and the administration of ketamine ($r=0.41$); on the sixth postoperative day, statistically significant positive correlations ($p<0.05$) were found between the acute pain score on the VAS and the administration of Omnopon ($r=0.77$) and acetaminophen ($r=39$). For the FLACC scale, statistically significant positive correlations ($p<0.05$) were found on the first postoperative day with the administration of Fentanyl ($r=0.26$), Promedol ($r=0.53$) and Paracetamol ($r=0.31$); on the third postoperative day with the administration of Promedol ($r=0.48$) and Paracetamol ($r=0.33$); on the sixth postoperative day with the administration of Paracetamol ($r=0.3$).

The mean ICU length of stay was 0.94±0.07 days, the mean surgical length of stay was 8.11±0.38 days, and the mean total hospital length of stay was 9.08±0.43 days. Statistically significant positive correlations ($p<0.05$) were found between the VAS acute pain score on the first day after surgery and the ICU length of stay ($r=0.39$) and the total hospital stay ($r=0.28$). These correlations remained positive on postoperative days 3 ($r=0.43$ and $r=0.48$) and 6 ($r=0.27$ and $r=0.23$).

In addition, the absolute levels of serum TLR4 in children at discharge (mean day 9.08±0.43), three and six months after surgery were examined (Fig. 1). The mean level of this membrane protein in children who underwent surgery for acute appendicitis was 18.13±0.41 pg/ml at discharge, 54.3±1.74 pg/ml three months after surgery, and 102.17 pg/ml six months after surgery ($p<0.001$ across all groups).

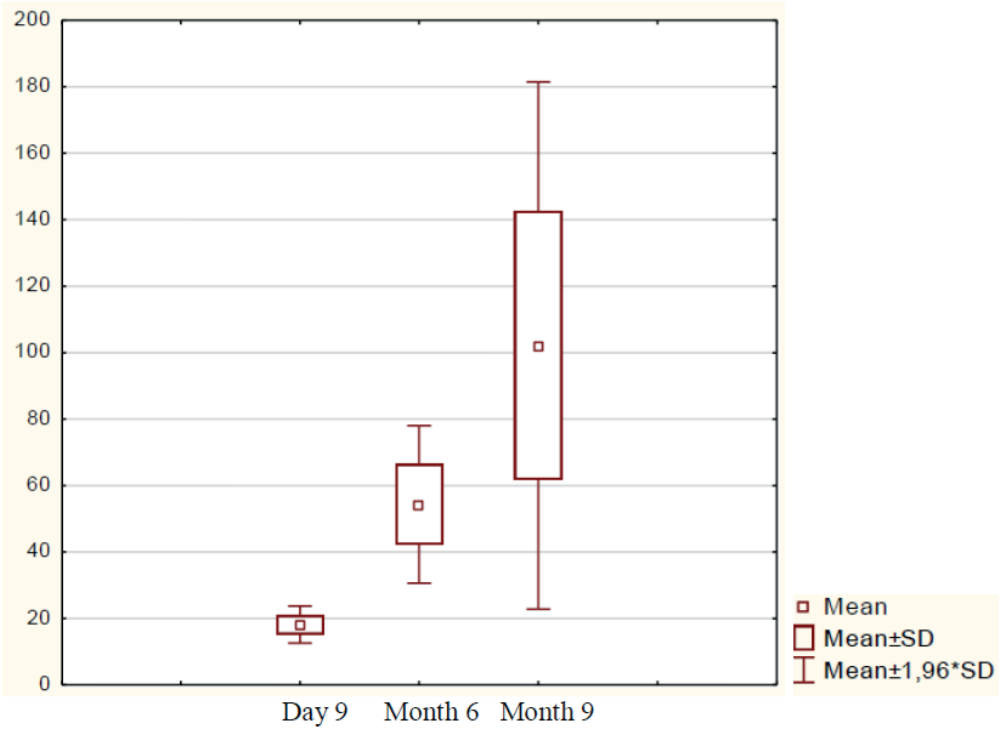

Fig. 1. Serum TLR4 level in pediatric patients (pg/ml), n=48

The mean acute pain score on the VAS was 3.08±0.13 points one day after surgery, 2.54±0.13 points three months after surgery, and 1.98±0.12 points six months after surgery ($p<0.001$ across all groups); the mean FLACC scale score was 3.39±0.12 points, 2.62±0.13 points, and 2.14±0.14 points, respectively ($p<0.001$ across all groups). A correlation between serum TLR4 levels and the given acute pain assessment scales is shown in Table 5.

Table 5

Correlation coefficients between acute pain assessment scores on the VAS and FLACC scale and serum TLR4 levels in children, $p<0.05$

Indicator	VAS			FLACC		
	Day 1	Day 3	Discharge	Day 1	Day 3	Discharge
TLR4 level at discharge, pg/ml	0.31	0.43	0.39	0.48	0.49	0.59
TLR4 level 3 months after surgery, pg/ml	0.46	0.55	0.47	0.63	0.63	0.64
TLR4 level 6 months after surgery, pg/ml	0.37	0.46	0.39	0.61	0.53	0.58

The mean serum CD40L level in children was 2213.9 [114.9; 4582.5] pg/mL during surgery, 2125.3 [79.4; 4582.5] pg/mL 12 hours after surgery, and 1508.4 [88.3; 3922.5] pg/mL on the day of discharge, p<0.05 in all groups (Fig. 2).

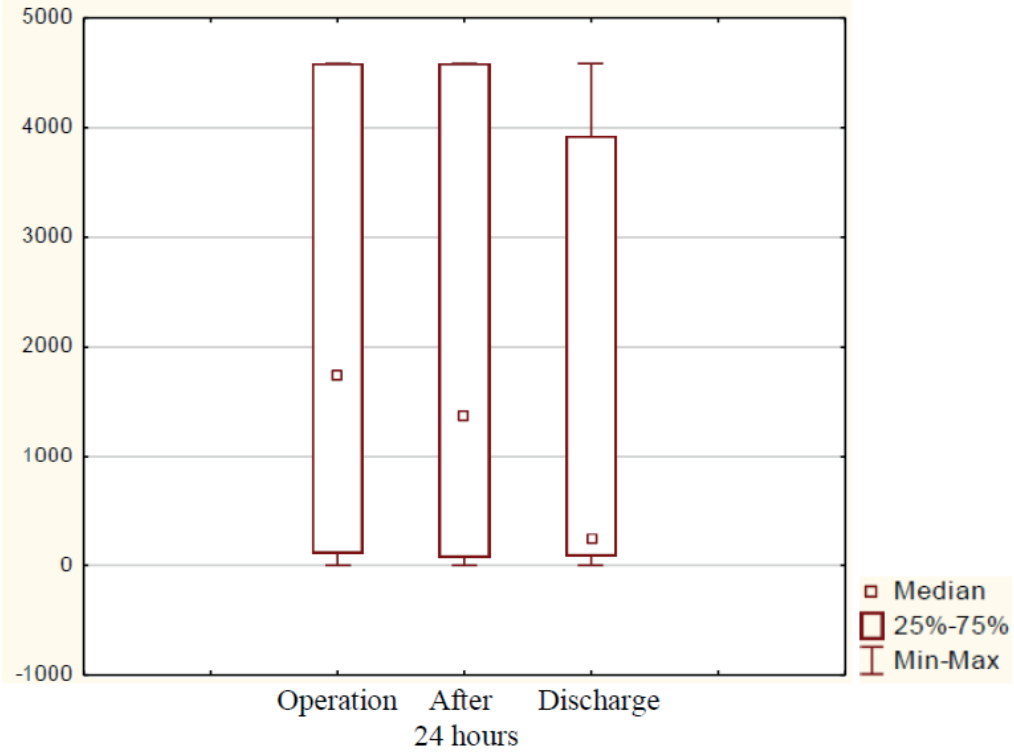

Fig. 2. Serum CD40L level in pediatric patients (pg/ml), n=30

The mean acute pain score on the VAS was 5.06 [3.0; 7.0] points within the first hours after surgery, 3.36 [3.0; 4.0] points at 24 hours after surgery, and 2.3 [2.0; 3.0] points at discharge; the mean FLACC scale score was 5.23 [3.0; 7.0] points, 3.23 [3.0; 3.0] points, and 2.2 [2.0; 2.0] points, respectively (p<0.001 in all groups). Correlations between serum CD40L levels and the acute pain scales are shown in Table 6.

Table 6

Correlation coefficients between acute pain assessment scores on the VAS and FLACC scale and serum CD40L levels in children, p<0.05

Indicator	VAS			FLACC		
	Surgery	24 hours after surgery	Discharge	Surgery	24 hours after surgery	Discharge
CD40L level during surgery, pg/ml	0.66	0.38	0.42	0.75	0.43	0.51
CD40L level 24 hours after surgery, pg/ml	0.68	0.49	0.43	0.78	0.46	0.58
CD40L level at discharge, pg/ml	0.75	0.38	0.37	0.67	0.53	0.42

Conclusions. Our study revealed various statistically significant differences between acute pain assessment on VAS and FLACC scale and clinical and paraclinical indicators in children operated for acute appendicitis at different postoperative intervals, showing very strong positive correlations (r=0.9-1. 0) between the given scales and heart rate, blood glucose levels; strong positive correlations (r=0.7-0.9) with total leukocyte count and ESR; moderate positive correlations (r=0.5-0.7) with serum TLR4 and CD40L levels; weak positive correlations (r<0.5) with DBP, SpO2 and administration of opioid and non-opioid analgesics. Positive correlations between acute pain assessment score on the VAS and FLACC scale and pro-inflammatory indicators are noteworthy, as it may support the theory of involvement of these markers in the generation of acute pain in the pediatric patient group. The results obtained indicate the potential for further exploration of the mechanisms underlying acute postoperative pain, the identification of markers related to nociception in chronic pain, and the development of preventive strategies for these conditions in pediatric patients.

Conflict of Interests: none.

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КЛІНІКО-ЛАБОРАТОРНІ ЗМІНИ МАРКЕРІВ БОЛЮ У ДІТЕЙ В ПІСЛЯОПЕРАЦІЙНОМУ ПЕРІОДІ

Я. В. Семкович

КНП «Івано-Франківська обласна дитяча клінічна лікарня Івано-Франківської обласної ради»
(м. Івано-Франківськ, Україна)

Резюме.

Післяопераційний біль у дітей до цього часу є суттєвою проблемою для педіатричної інтенсивної терапії, що може бути пов'язано з недосконалим алгоритмом його менеджменту. Тривалий післяопераційний біль призводить до подовження термінів госпіталізації, підвищення вартості лікування, збільшення часу реабілітації та тривалості застосування опіоїдів. Неадекватне періопераційне знеболення може спричинити велику кількість післяопераційних ускладнень, прогнозування яких за допомогою загально прийнятих клінічних, лабораторних та інструментальних показників на сьогодні не вдається.

Метою даного дослідження було оцінити клініко-лабораторні зміни у дітей, яким проведено операції на органах черевної порожнини, та їх кореляційний зв'язок зі шкалами для оцінки гострого болю.

Матеріал та методи дослідження. У дослідженні взяли участь 83 дитини віком 7-18 років, яким проводилось оперативне втручання на органах черевної порожнини із застосуванням загальноприйнятого опіоїдного знеболення.

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Критерії включення: вік 7-18 років; покази до проведення оперативного втручання з приводу гострого апендициту; ступінь анестезіологічного ризику за шкалою ASA (American Society of Anesthesiologists) I-II ступенів; згода батьків/опікунів на залучення дитини у дослідження.

Для визначення інтенсивності гострого болю у дітей використовували візуально-аналогову шкалу (ВАШ) та шкалу FLACC, для оцінки основних вітальних функцій визначали частоту серцевих скорочень, частоту дихання, систолічний та діастолічний артеріальний тиск, рівень сатурації крові. Також проводили визначення лабораторних показників: рівня лейкоцитів, глюкози в крові, швидкості осідання еритроцитів, рівень білків TLR-4 та CD40L.

Усі клінічні та лабораторні дослідження проводилися відповідно до Гельсінської декларації Всесвітньої медичної асоціації «Етичні принципи медичних досліджень за участю людини як об'єкт дослідження» (протоколу комісії з біоетики № 2 від 24.02.2022 року).

Статистичний аналіз здійснювали на персональному комп'ютері за допомогою комп'ютерної програми Statistica 10 з використанням методів параметричної та непараметричної статистики.

Робота є фрагментом науково-дослідної роботи кафедри дитячих хвороб ПО ІФНМУ: «Стан здоров'я та особливості адаптації дітей Прикарпаття із соматичними захворюваннями, їх профілактика», номер державної реєстрації 0121U111129, терміни виконання 2021-2026 рр., автор є співвиконавцем теми.

Результати дослідження. Середній вік дітей склав 13,8±0,23 роки, а вага – 40,9 ±1,6 кг. Оцінка гендерної приналежності не виявила різниці між хлопчиками та дівчатками (55, 4 та 44,6 %, $p > 0,05$).

У ході дослідження встановлено дуже сильні позитивні кореляції ($r = 0,9$-$1,0$) між больною оцінкою гострого болю за шкалами ВАШ та FLACC та частотою серцевих скорочень, рівнем глюкози у крові; сильні позитивні кореляції ($r = 0,7$-$0,9$) – з загальним рівнем лейкоцитів та швидкістю осідання еритроцитів; позитивні кореляції середньої сили ($r = 0,5$-$0,7$) – з рівнями TLR-4 та CD40L у крові, позитивні кореляції слабкої сили ($r < 0,5$) – з рівнем діастолічного артеріального тиску, SpO_2, призначенням наркотичних та ненаркотичних анальгетиків.

Висновок. Встановлені позитивні кореляційні залежностей між больною оцінкою гострого болю ВАШ і FLACC з прозапальними показниками може підтверджувати теорію участі даних маркерів у формуванні гострого болю у педіатричної групи пацієнтів. Але необхідно продовжувати дослідження щодо вивчення механізмів формування гострого післяопераційного болю, виявлення маркерів ноцицепції хронічного болю та розробки шляхів профілактики даних станів у дітей.

Ключові слова: діти; гострий післяопераційний біль; система CD40L; TLR-4; FLACC; візуально-аналогова шкала оцінки болю.

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