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Study of the polymorphism of the ADRB2 molecular structure and its influence on the development of chronic postsurgical pain in children

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Introduction. Pain is a signal to any aggression that leads to cellular damage and requires a defensive response. Uncontrolled acute perioperative visceral pain can lead to the development of pain chronicity. By studying the characteristics of chronic pain, some scientists have identified relationships with single-nucleotide polymorphisms of the beta2-adrenergic receptor (*ADRB2*) gene.

Purpose – to study the dependence of pain expression in the postoperative period in children on the polymorphism of the molecular structure of the *ADRB2* receptor.

Materials and methods. The study involved 42 children (20 boys and 22 girls) aged 7 to 18 years who were treated in the surgical department in 2020–2022 for acute appendicitis and peritonitis.

Results. Based on the results of examining all the subjects under study, 13 children had the Arg16Gly polymorphism, 15 children had the *Arg16Gly* polymorphic variant, and 14 children were diagnosed with the homomorphic *Gly16Gly* polymorphism in the *ADRB2*. The data obtained confirmed the trend of the preliminary analysis and proved better body response to pain relief and reduced pain intensity in individuals with the *Arg16Arg* variant of the *ADRB2*.

Analysis of the dependence between the polymorphism of the *ADRB2* molecular structure and Visual Analogue Scale (VAS) scores in children in the postoperative period proved that the presence of Arg in the receptor phenotype had a strong negative correlation with the VAS score on discharge day ($r=-0.822$, $p<0.001$), while the presence of Gly in the receptor phenotype had a strong positive correlation with the Visual Analogue Scale score on discharge day ($r=0.814$, $p<0.001$). In regression analysis, the presence of *Gly* in the receptor phenotype was associated with a 1.917-fold increase in the VAS score at hospital discharge (OR: 1.917; 95% CI: 1.448–2.385; $p<0.001$).

Conclusions. The presence of the homomorphic *Arg16Arg* variant of the *ADRB2* in children who underwent anterior abdominal wall surgery was accompanied by rapid response to analgesics.

The research was carried out in accordance with the principles of the Helsinki Declaration. The study protocol was approved by the Local Ethics Committee of the participating institution. The informed consent of the patient was obtained for conducting the studies.

No conflict of interests was declared by the authors.

Keywords: chronic pain, children, polymorphism, *ADRB2*.

Вивчення поліморфізму молекулярної структури рецептора ADRB2 у дітей після операцій на передній черевній стінці

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Вступ. Біль – це сигнал на будь-яку агресію, яка призводить до пошкодження клітин і потребує відповіді в якості захисної реакції. При неконтрольованому гострому періопераційному вісцеральному болю можливий розвиток хронізації болю. Вивчаючи осо-

бливості хронічного болю, деякі вчені виявили взаємозв'язки з однонуклеотидними поліморфізмами гена бета2-адренергічного рецептора (*ADRB2*).

Мета – вивчити залежність експресії болю в післяопераційний період у дітей від поліморфізму молекулярної структури рецептора *ADRB2*.

Матеріали та методи. У дослідженні взяли участь 42 дитини (20 хлопчиків і 22 дівчинки) віком від 7 до 18 років, які проходили лікування в хірургічному відділенні у 2020–2022 рр. з приводу гострого апендициту, перитоніту.

Результати. Встановлено, що 13 із досліджуваних пацієнтів мали варіант поліморфізму *Arg16Arg*, 15 – *Arg16Gly*, 14 дітей – гомоморфічний варіант поліморфізму *Gly16Gly*. Отримані дані підтверджують кращу відповідь організму на знеболювання та зменшення інтенсивності болю в осіб із морфологічним варіантом рецептора *ADRB2 Arg16Arg*.

Аналіз залежності показників візуальної аналогової шкали (ВАШ) від поліморфізму молекулярної структури рецептора *ADRB2* в післяопераційний період у дітей довів, що наявність *Arg* у фенотипі рецептора мала дуже сильну негативну кореляцію з показником ВАШ на етапі виписки (r=-0,822, p<0,001); наявність *Gly* у генотипі мала дуже сильну позитивну кореляцію з показником ВАШ на етапі виписки (r=0,814; p<0,001). У регресійному аналізі наявність *Gly* у фенотипі рецептора асоціювалася з вищим на 1,917 показником ВАШ на етапі виписки (ВШ=1,917; 95% ДІ: 1,448–2,385; p<0,001).

Висновки. Наявність комбінації гомоморфічного варіанта рецептора *ADRB2 Arg16Arg* у дітей, оперованих на передній черевній стінці, супроводжується швидкою відповіддю на знеболювальні препарати.

Дослідження виконано відповідно до принципів Гельсінської декларації. Протокол дослідження ухвалено Локальним етичним комітетом зазначеної в роботі установи. На проведення досліджень отримано інформовану згоду батьків, дітей.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: хронічний біль, діти, поліморфізм, рецептор *ADRB2*.

Introduction

Pain is a subjective experience with an objective biochemical basis causing ongoing challenges for healthcare professionals around the world [28]. Pain can be characterized as a conscious response to a sensory stimulus that activates nociceptive afferents and a mental projection of that stimulus onto a particular body part. Pain is a sensation that prompts a person to avoid dangerous situations and protect damaged tissues during wound healing. The International Association for the Study of Pain (IASP) defines pain as «an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage» [12]. Pain is a signal for any aggression resulting in cell damage and requires a response as a defensive reaction. Pain is a stable criterion for assessing quality of life in both surgical and therapeutic patients. The adequacy of postoperative pain management ranges between 51–56% [2].

Postoperative pain is not adequately managed in more than 80% of patients in the USA. Inadequate postoperative pain management is associated with increased morbidity, reduced function and quality of life, long-term recovery, and prolonged opioid use [9].

Inadequate perioperative pain management can result in a variety of cardiovascular (arterial hypertension, arrythmia, acute myocardial ischemia), respiratory (reduced lung capacity, atelectasis, hypostatic pneumonia, hypoxia), gastrointestinal (gastroparesis, bacterial translocation), and central nervous system (chronic pain syndrome, hyperalgesia) complications, as well as coagulation disorders (hypercoagulation, deep vein thrombosis, pulmonary embolism), depression [29].

The main conceptual issue in understanding pain is the distinction between acute, chronic and cancer pain [19]. Although chronic pain is a very versatile category, it is called the 'disease on its own' [18], and therefore, the related concepts of chronic pathological and maladaptive pain should be understood in this context [6]. Compared to pain signals that come from the skin and can be well localized, pain that stems from the internal organs, muscles, and bones is described as diffuse, often poorly localized. Visceral pain is more unpleasant than somatic pain [8] and is accompanied by greater fear [13]. Hence, bone pain and ischemic pain are accompanied by visceral pain [13,14]. Ischemic pain and bone pain are believed to be transmitted through afferent nerve fibers which, like visceral pain, are anatomically associated with sympathetic afferent fibers passing along the blood vessels [15]. The transduction, modulation and perception of visceral pain are very similar to those of somatic pain, with a few exceptions; however, their transmission differs significantly [10]. When assessing the effect of visceral pain on the patient's postoperative recovery, an interindividual variability in visceral pain intensity should be considered [3]. Depending on the procedure performed, visceral or somatic pain may be dominant. For instance, after laparoscopic inguinal hernia repair, the most intense pain was diagnosed on the day of surgery, with visceral pain significantly dominating over superficial pain [27]. As primary somatic pain subsides throughout the first postoperative days, visceral pain intensity increases, obviously due to the irritation and inflammation of the parietal peritoneum. In uncontrolled acute perioperative visceral pain, its transformation into chronic pain is possible. Prolonged aggressive

stimulation of the internal organs and the peripheral sensitization of visceral nociceptors can result in central sensitization [24].

When studying chronic pain, some researchers found its association with single nucleotide polymorphisms (SNPs) of the beta2-adrenergic receptor (*ADRB2*) gene. The *ADRB2* gene encodes beta-2-adrenergic receptor which is a member of the G protein-coupled receptor and the main receptor mediating the responses of sympathetic neurotransmitters [16,21]. The β2-adrenergic receptor is expressed within the nociceptive system [11,30], including the superficial dorsal horn neurons of the spinal cord [17], which plays an important role in pain transmission [1,20]. Several *ADRB2* SNPs were studied in temporomandibular joint pain [5]. The haplotypes were found to correlate with *ADRB2* expression and resting blood pressure as well. In musculoskeletal disorders, there was found a relationship between the H1-H1 haplotype, *ADRB2* rs2053044 and chronic pain [25].

The purpose of the study – to investigate the dependance between the polymorphism of the *ADRB2* molecular structure and pain expression in children in the postoperative period.

Materials and methods of the research

The study included 42 (20 boys, 22 girls) children at the age of 7–18 years who were treated for acute appendicitis, peritonitis at the Surgical Department and the Department of Anesthesiology and Intensive Care of a Communal Non-Profit Enterprise «Ivano-Frankivsk Regional Children's Clinical Hospital of Ivano-Frankivsk Regional Council», during 2020–2022. Appendicitis and peritonitis were diagnosed and treated according to the clinical protocol of the Ministry of Health of Ukraine No. 88 dated March 30, 2004 [26]. A total of 11 children were excluded from the study due to: parental refusal 7 children), repeated relaparotomies on the background of intestinal obstruction 1 child), moving abroad 3 children). Finally, 42 children continued their participation in the study.

All children underwent anterior abdominal wall surgery under general anesthesia. Postoperative pain management included opioids and nonsteroidal anti-inflammatory drugs, if needed. The assessment of acute pain and the quality of pain management was carried out by means of the Visual Analogue Scale (VAS). The indicators of the VAS were determined in all children 12, 24, 72 hours after surgery and at hospital discharge. The Neuropathic Pain Diagnostic Questionnaire DN4 (Douleur Neuropathique 4 Questions) and the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Pain Scale (Bennett M, 2001) were used to assess the presence of chronic or neuropathic pain. The indicators of the DN4 and LANSS pain scale were determined three and six months after surgery, respectively.

Inclusion criteria were children at the age of 7–18 years who underwent anterior abdominal wall surgery, ASA grades I-II, with the mandatory parental consent to involve their child in clinical research. *Exclusion criteria* included children less than 7 years old; those with ASA grade III or higher, mental disorders, neoplasms, or tumors, acute or inflammatory processes of any etiology and localization, sepsis, shock; those who previously underwent surgery on the lower abdomen; those who experienced pain for 6 months prior to surgery; those who refused to participate in the research; children whose parents refused to give consent and children who gave no consent.

To establish the polymorphism of the *ADRB2* molecular structure, whole blood was taken for genetic study by real-time polymerase chain reaction taken from all the patients (Vinnytsia scientific, clinical diagnostic polymerase chain reaction laboratory, Certificate of Accreditation No. 051/15).

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». According to the Law, prior to a subject's participation in the study, a written informed consent form was signed by each subject (parents / adult guardians). The manuscript was approved by the Ethics Committee of the Communal Non-Profit Enterprise «Ivano-Frankivsk Regional Children's Clinical Hospital of Ivano-Frankivsk Regional Council» as evidenced by an Excerpt from the Minute of the Committee Meeting No. 2 dated March 15, 2022.

The results obtained were statistically processed using the IBM SPSS Statistics Version 26.0 for Windows. Descriptive statistics were determined for each interval variable and presented as the mean (M) ± standard deviation (SD). To determine whether sample data were normally distributed, the Kolmogorov–Smirnov test was used. To compare the means of two independent groups of patients when the distribution of the variables was normal or not normal, there were used the Mann–Whitney U test and the Independent Samples t-test, respectively. To compare two paired samples in case of non-normal data distribution, we used the Wilcoxon test; to compare two paired samples in case of normal data distribution, the Student's t-test was used. To compare three and more independent variables, the Kruskal–Wallis One-Way ANOVA test was used. To assess the relationship between the variables in case of non-normal data distribution and/or

Table 1
VAS scores at different time periods after surgery

VAS	Group I *Arg16Arg* (n=13)	Group II *Arg 16Gly* (n=15)	Group III *Gly 16Gly* (n=14)	P
VAS, 12 hours after surgery	4.69±0.18#	4.77±0.2	4.85±0.19	0.848
VAS, 24 hours after surgery	4.69±0.4#	4.69±0.37	4.77±0.36	0.986
VAS, 72 hours after surgery	4.54±0.24#	4.77±0.2	4.85±0.19	0.573
VAS, at hospital discharge	2.85±0.1	3.92±0.24*	4.77±0.12**	<0.001

Notes: * – a significant difference between the Group I and the Group II (p<0.001); ** – a significant difference between the Group I and the Group III (p<0.001); # – a significant difference in the Group I between the VAS score 12, 24, 72 hours after surgery and at hospital discharge (p<0.001).

ordinal variables, the Spearman's Rank correlation coefficient was applied; in case of normally distributed data, the Pearson correlation coefficient was used. To identify predictors for dichotomous dependent variables, we used a binomial logistic regression with the «Enter» method; to identify predictors for continuous dependent variables, we applied a stepwise liner regression. Only predictors demonstrating weak, strong, or moderate positive and negative correlations with a dependent variable, i.e., the Spearman's or Pearson correlation coefficient ≥0.2, were included in the regression model. Regression analysis results were presented as an odds ratio (OR), 95% confidence intervals (CI). A p-value less than 0.05 was considered statistically significant.

Results of the study

Based on the results of examining all the subjects under study, 13 (31%) children had the *Arg16Gly* polymorphism of the *ADRB2* and, therefore, they were assigned to the Group I; the *Arg16Gly* polymorphic variant of the *ADRB2* was diagnosed in 15 (36%) children who were assigned to the Group II; the Group III included 14 (33%) children with the homomorphic *Gly16Gly* polymorphism in the *ADRB2*. The average age of children was as follows: the Group I – 9.17±0.57 years, the Group II – 10.42±0.9 years, the Group III – 11.12±0.74 years (p=0.192).

The relationship between the results of the *ADRB2* polymorphism and the indicators of pain management quality and the presence of acute pain assessed using the VAS was primarily analyzed (Table 1).

There was determined a statistically significant difference in the VAS score at hospital discharge (p<0.001). The Fisher's least significant difference (LSD) test for pairwise comparison of groups found that on discharge day, the Group I had a significantly lower VAS score as compared to the Group II and the Group III (p<0.001). This group of individuals had a homomorphic variant of arginine molecule in the *ADRB2*. According to Table 1, the VAS score reduced by 1.65 times from the first 12 hours after surgery to hospital discharge. This might indicate that children with such polymorphic variant responded to analgesia better as compared to others. During treatment, VAS scores changed as follows: 4.69±0.18 twelve hours after surgery with a tendency towards reduction 72 hours after surgery and at hospital discharge (4.54±0.24 and 2.85±0.1, respectively, p<0.001).

Children of the Group II had a polymorphic *ADRB2* variant containing arginine and glutamine molecules, i.e., a heteromorphic *Arg16Gly* variant. At hospital discharge, the Group II showed a statistically higher VAS score as compared to the Group I (p<0.001). The VAS score tended to decrease between 12 and 24 hours after surgery (Table 1); however, up to 72 hours of follow-up, it increased from 4.69±0.37 to 4.77±0.2. Although acute pain reduced by 1.2 times on discharge day, no VAS scores were normal.

The Group III included children with a homomorphic *ADRB2* variant containing glutamine molecules. Analysis of the quality of pain management and the presence of acute pain in this group revealed no positive effect of analgesia, i.e., pain relief both within the first hours after surgery and after discharge. The VAS score ranged from 4.85±0.19 within the first 12 hours after surgery to 4.77±0.12 on discharge day, remaining at these levels during treatment (24 hours after surgery – 4.77±0.36 and 72 hours after surgery – 4.85±0.19) (Fig. 1).

There was a strong negative correlation between the presence of *Arg* in the receptor phenotype and the VAS score on discharge day (r=-0.822, p<0.001). The presence of *Gly* in the receptor phenotype had a strong positive correlation with the VAS score on discharge day (r=0.814, p<0.001), that might indicate various tropism for pain relief depending on the polymorphism and variants of the *ADRB2*.

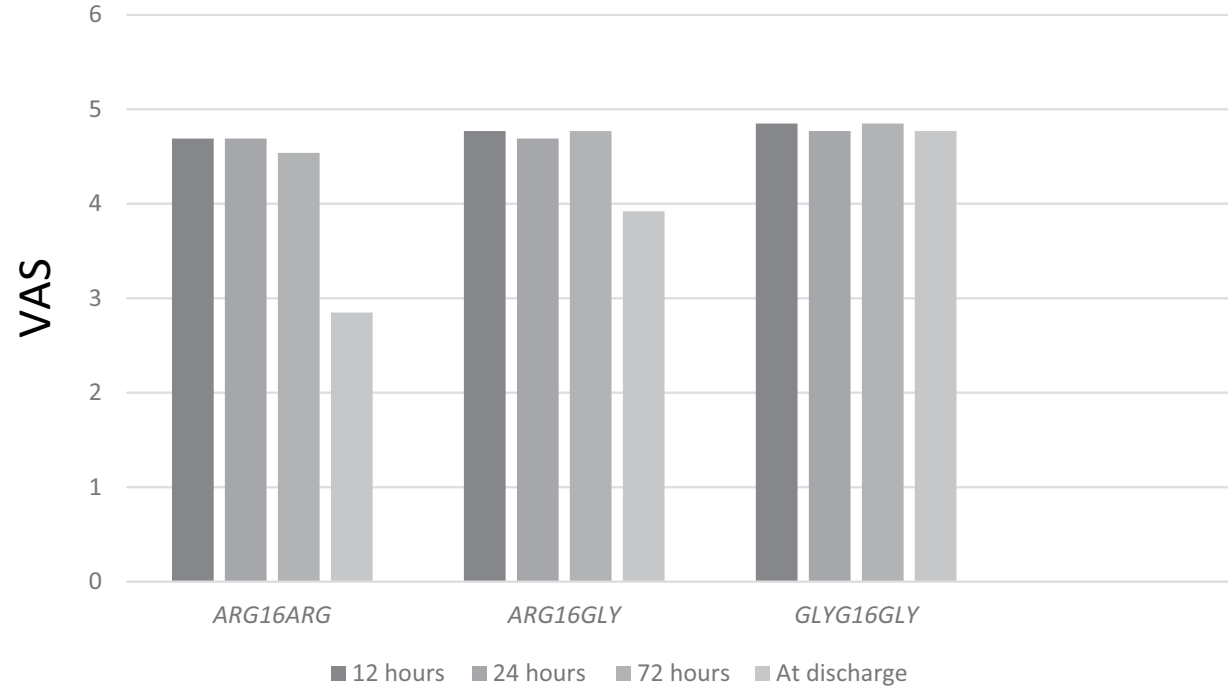

Fig. 1. VAS scores depending on the length of hospital stay and *ADRB2* phenotype

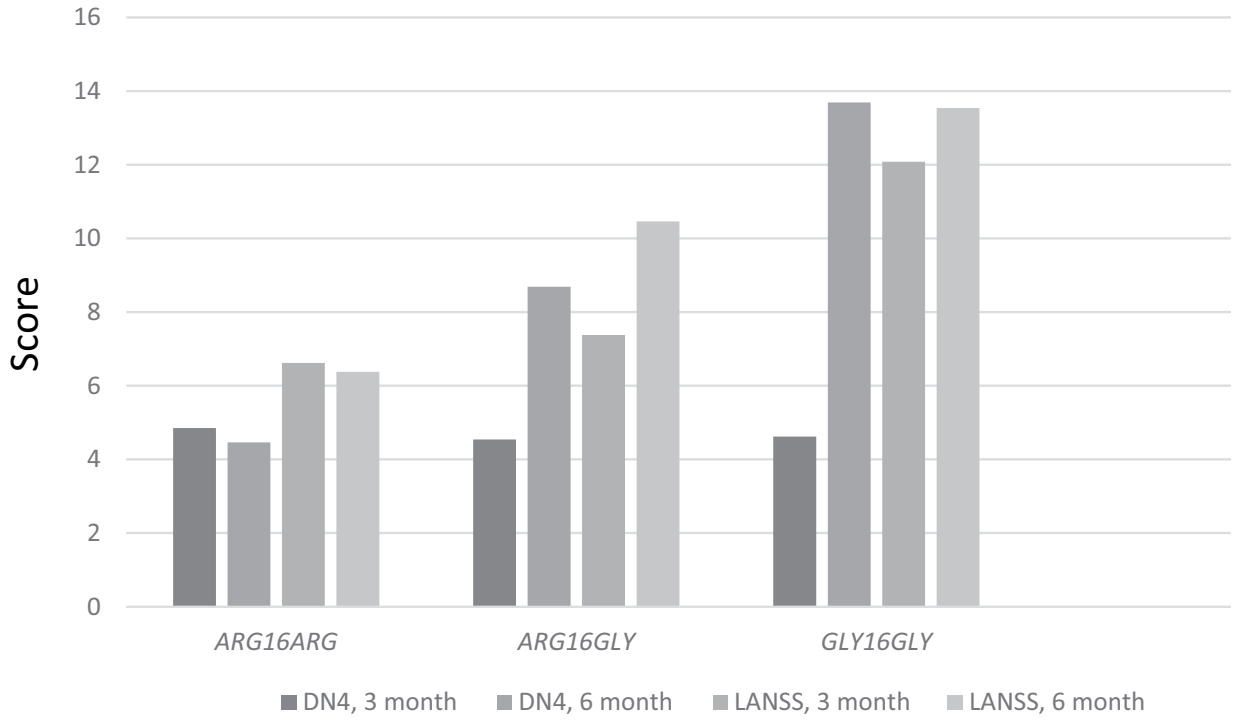

Fig. 2. Indicators of the DN4 and LANSS pain scale three and six months after surgery

In regression analysis, the presence of *Gly* in the receptor phenotype was associated with a 1.917-fold increase in the VAS score at hospital discharge (OR: 1.917; 95% CI: 1.448–2.385; p<0.001).

Next, the relationship between the indicators of the DN4 and LANSS pain scale and the *ADRB2* polymorphism was studied (Fig. 2).

The comparison of the studied groups revealed a statistically significant difference in the DN4 indicator six months after surgery and the LANSS pain scale indicator three and six months after surgery (p<0.001). The Fisher's LSD test for pairwise comparison of groups found a statistically significant difference in the DN4 indicator six months after surgery between all the studied groups

Table 2
Chronic pain scales

Pain scales	Group I *Arg16Arg* (n=13)	Group II *Gly16Gly* (n=15)	Group III *Arg16Gly* (n=14)	P
DN4, 3 months after surgery	4.85±0.19	4.54±0.18	4.62±0.18	0.48
DN4, 6 months after surgery	5.46±0.42	8.69±0.78*	13.69±0.38**	<0.001
LANSS pain scale, 3 months after surgery	6.62±0.66	7.38±0.76	12.08±0.31**	<0.001
LANSS pain scale, 6 months after surgery	6.38±0.5	10.46±0.35*	13.54±0.33**	<0.001

Notes: * – a significant difference between the Group I and the Group II (p<0.001); ** – a significant difference between the Group I and the Group III (p<0.001).

(p<0.001). There was a statistically significant difference in the LANSS pain scale indicator three months after surgery between the Group I and the Group III (p<0.001), as well as the Group II and the Group III (p<0.001). The Fisher's LSD test for pairwise comparison of groups found a statistically significant difference in the LANSS pain scale indicator six months after surgery between all the studied groups (p<0.001) (Table 2).

The data obtained confirmed the trend of the preliminary analysis and proved better body response to pain relief and reduced pain intensity in individuals with the *Arg16Arg* variant of the *ADRB2.* Children of the Group II with the *Arg16Gly* variant of the *ADRB2* (one arginine molecule and one glutamine molecule) felt pain relief more quickly (as evidenced by VAS scores) as compared to children of the Group III with the homomorphic *Gly16Gly* polymorphism in the *ADRB2*, but much later than patients of the Group I.

Discussion of the research

Chronic pain is pain that occurs on more than 50% of the days within 6 months, or pain that persists for at least three months. This syndrome is one of the most common pathological conditions. Chronic pain significantly affects daily activities, reduces learning ability and life quality in children [22]. The study of its prevalence, timely diagnosis, and appropriate management are an urgent priority [4,7,23].

Risk factors for chronic postoperative pain are found in the preoperative, intraoperative, and postoperative periods and involve the following six fields: genetic, demographic, psychosocial, pain, clinical, and surgical factors. Demographic factors such as young age and female gender, as well as psychological factors such as anxiety, depression, critical stage of the disease, fear of surgery, significantly affect the incidence of chronic postoperative pain. In children at the age of 8–18 years, 'parental pain catastrophizing' was the main risk factor for the development of chronic postoperative pain.

In the Group I, there was no statistically significant increase in the DN4 (p=0.163) and LANSS pain scale (p=0.437) indicators. However, a statistically significant increase in these indicators was observed in children of the Group II (DN4 (p=0.002), LANSS pain scale (p=0.009)) and the Group III (DN4 (p=0.001), LENSS (p=0.009)).

There was a strong negative correlation between the presence of *Arg* in the receptor phenotype and the DN4 indicator six months after surgery (r=-0.824, p<0.001), as well as the LANSS pain scale indicator three (r=-0.690, p<0.001) and six (r=-0.905, p<0.001) months after surgery. In contrast, the presence of *Gly* in the receptor phenotype had a strong positive correlation with the DN4 indicator six months after surgery (r=0.832, p<0.001), as well as the LANSS pain scale indicator three (r=0.700, p<0.001) and six (r=0.906, p<0.001) months after surgery.

In regression analysis, the presence of *Gly* in the receptor phenotype was associated with an 8.25-fold increase in the DN4 indicator three months after surgery (OR: 9.25; 95% CI: 6.389–10.111; p<0.001), a 5.583-fold increase in the LANSS pain scale indicator three months after surgery (OR: 5.583; 95% CI: 3.580–7.587; p<0.001)], a 7.417-fold increase in the LANSS pain scale indicator six months after surgery (OR: 7.417; 95% CI: 6.190–8.643; p<0.001).

Analysis of the dependance between the polymorphism of the *ADRB2* molecular structure and VAS scores in children in the postoperative period proved that the presence of *Arg* in the receptor phenotype had a strong negative correlation with the VAS score on discharge day (r=-0.822, p<0.001). The presence of *Gly* in the receptor phenotype had a strong positive correlation with the VAS score on discharge day (r=0.814, p<0.001). In regression analysis, the presence of *Gly* in the receptor phenotype was associated with a 1.917-fold increase in the VAS score at hospital discharge (OR: 1.917; 95% CI: 1.448–2.385; p<0.001). The same trend was observed when analyzing the DN4 and LANSS pain scale indicators.

Conclusions

Polymorphism of the *ADRB2* molecular structure can serve as a pathognomonic marker for pain intensity and analgesic tolerance.

The presence of the homomorphic *Arg16Arg* variant of the *ADRB2* in children who underwent anterior abdominal wall surgery was accompanied by rapid response to analgesics, as evidenced by reduced pain intensity.

The presence of the *Arg16Gly* variant of the *ADRB2* or the homomorphic *Gly16Gly* variant of the *ADRB2* in children who underwent anterior abdominal wall surgery was accompanied by an inadequate response to pain management and high VAS scores indicating high pain intensity.

The presence of the *Arg16Gly* variant of the *ADRB2* or the homomorphic *Gly16Gly* variant of the *ADRB2* in children who underwent anterior abdominal wall surgery was accompanied by higher incidence of chronic pain syndrome.

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