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PREVENTION OF HYPERALGESIA
IN CHILDREN WHEN USING VARIOUS
ANESTHESIA TECHNIQUES

Ya. V. Semkovych¹, D. V. Dmytriiev²

Communal Non-Profit Enterprise “Ivano-Frankivsk Regional Children’s Clinical Hospital of Ivano-Frankivsk Regional Council” (Ivano-Frankivsk, Ukraine)¹
Vinnytsia National Pirogov Memorial Medical University (Vinnytsia, Ukraine)²

Summary

Introduction. Opioid-induced hyperalgesia is characterized by a paradoxical response whereby a patient receiving opioids for pain management could actually become more sensitive to certain painful stimuli. Regional anesthesia can also impact central sensitization and reduce hyperalgesia after surgery.

The objective of the study was to determine the method of preventing hyperalgesia in the early postoperative period when using different analgesic regimens in children after anterior abdominal wall surgery.

Materials and Methods. The study included 87 children at the age of 7-18 years who underwent anterior abdominal wall surgery using different analgesic techniques. Group I included 33 children who underwent anterior abdominal wall surgery under general anesthesia using fentanyl. Group II comprised 27 children who underwent anterior abdominal wall surgery under general anesthesia using the transversalis fascia plane block (TFPB). Group III involved 27 children who underwent anterior abdominal wall surgery under general anesthesia using the TFPB, combined with the quadratus lumborum block 4 (QLB-4) via a single injection.

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 February 24, 2022.

The results obtained were statistically processed using statistical measures of variation, correlation analysis, Student’s t-test. Differences were considered statistically significant at $p < 0.05$. The proportions were statistically compared by a z-test.

The study is a fragment of the research project of the Department of Children Diseases of Postgraduate Medical Education Faculty, Ivano-Frankivsk National Medical University “Health Status and Adaption of Children from the Pre-Carpathian Region with Somatic Diseases, Their Prevention” 2021-2026, state registration number 0121U111129; the author is a co-researcher.

Results. In most (48.5 %) patients of Group I, the response to stimulation occurred only when applying pressure forces of 8 and 10 g, while the motor response was observed to stimulation with a pressure force of 8 g, with the FLACC scale score of 5.1 ± 0.3 , indicating insufficient pain threshold and potential development of opioid-induced hyperalgesia in the early postoperative period. In patients of Group II and Group III, the response to stimulation occurred when applying a pressure force of 8 g and the FLACC scale scores were 2.9 ± 0.27 and 2.4 ± 0.32 , respectively ($p < 0.05$).

Conclusions. The results obtained confirmed the benefits of using regional anesthesia techniques in combination with conventional analgesia.

Keywords: Hyperalgesia; Children; Regional Anesthesia; Myofascial Block.

Introduction

Opioid-induced hyperalgesia (OIH) is nociceptive sensitization after acute or chronic exposure to opioids. OIH is characterized by a paradoxical response whereby a patient receiving opioids for pain management could actually become more sensitive to certain painful stimuli [1, 2]. The precise molecular mechanism of OIH is not yet understood. This process is believed to result from neuroplastic changes in the peripheral and central nervous systems leading to sensitization of pronociceptive pathways. The main mechanisms of developing OIH are associated with the central glutaminergic system, spinal dynorphins, descending facilitation, genetic mechanisms as well as decreased reuptake and increased nociceptive

response. However, the central glutaminergic system is considered as the most common mechanism of OIH development. Another hypothesis suggests that n-methyl-D-aspartate (NMDA) receptors are involved in the activation/inhibition of glutamate transport, changes in calcium-regulated intracellular protein kinase C, cross talk of neural mechanisms of pain and tolerance. OIH should be suspected when the effect of opioid treatment wears off in the absence of disease progression, especially in the context of unexplained pain or diffuse allodynia unrelated to original pain, and elevating pain levels with increasing opioid doses [3].

The data on the clinical prevalence of OIH are lacking. Several studies on OIH development in the

perioperative period have primarily focused on the use of short-acting phenylpiperidine and piperidine opioids such as remifentanyl, alfentanil, and fentanyl, paying less attention to phenanthrene opioids such as morphine and hydromorphone [4-7]. Clinical differentiation of OIH and opioid tolerance remains challenging without an opioid dose reduction. Several clinical trials have demonstrated that pain management can be improved by reducing the opioid dosage, and hyperalgesia has often been described as a result of chronic opioid therapy [8].

Central factors, including the regulation of the central glutamergic system and NMDA receptors [9] as well as microglial activation [10], are considered important factors of OIH development. Activation of peripheral opioid receptors results in hyperalgesia, priming of prostaglandin, and changes in the function of transient receptor potential channels. It is important to note that the same pathways involved in OIH are also implicated in the development of opioid tolerance, opioid analgesia, and chronic pain [11].

OIH should be differentiated from opioid tolerance, opioid withdrawal syndrome, and opioid use disorder [12]. OIH is a state of increased nociception associated with acute or chronic exposure to opioids, whereas opioid tolerance refers to a pharmacological effect in which a higher dose of opioids is required to achieve the desired analgesic effect. Opioid withdrawal syndrome is a collection of clinical symptoms that occur due to discontinuing opioid use [13, 14]. The most effective approach to manage OIH is prevention. The perioperative period is associated with high levels of opioid exposure. OIH can be prevented in the peri-, intra-, and postoperative periods [15-18]. A retrospective study revealed that higher doses of intraoperative fentanyl (>3 g/kg) were associated with an accelerated onset of postsurgical pain, indicating acute OIH [19].

Regional anesthesia can also impact central sensitization and reduce hyperalgesia after surgery. In addition to reducing acute postsurgical pain, local anesthetics reduce acute inflammation, early cytokine production, and central markers of pain sensitization [20, 21]. Studies indicate that regional anesthesia should be used before surgery to achieve intraoperative pain relief and reduce intraoperative opioid use, thus reducing the risk of central sensitization and OIH [22]. Some authors suggest that the timing of regional anesthesia - preoperatively, intraoperatively, or postoperatively, is less significant compared to the application of regional analgesia in the acute postoperative period [23, 24]. Local anesthetics have been found to act as NMDA receptor antagonists; therefore, their use in regional anesthesia may contribute to the treatment and prevention of OIH [25-31].

The objective of the study was to determine the method of preventing hyperalgesia in the early postoperative period using different analgesic regimens in children after anterior abdominal wall surgery.

Materials and Methods

The study included 87 (46 boys and 41 girls) children at the age of 7-18 years who were treated at

the surgical department of a Communal Non-Profit Enterprise "Ivano-Frankivsk Regional Children's Clinical Hospital of Ivano-Frankivsk Regional Council", Ivano-Frankivsk, Ukraine, and underwent anterior abdominal wall surgery with different analgesic techniques during 2020-2022. Inclusion criteria were children with appendicitis ASA grades I-II at the age of 7-18 years, with the mandatory parental consent to involve their child in clinical research. The patients were randomly selected based on inclusion criteria. Surgery was performed using an open approach, with an incision on the anterior abdominal wall. Exclusion criteria included children under 7 years of age; those with ASA grade III or higher, mental disorders, neoplasms, or tumors, sepsis, shock; those who previously underwent lower abdominal surgery; those who experienced pain for six 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. All children were divided into 3 groups: Group I included 33 children who underwent anterior abdominal wall surgery under general anesthesia using fentanyl; Group II comprised 27 children who underwent anterior abdominal wall surgery under general anesthesia using the transversalis fascia plane block (TFPB); Group III involved 27 children who underwent anterior abdominal wall surgery under general anesthesia using the TFPB, combined with the quadratus lumborum block 4 (QLB-4) via a single injection. General anesthesia included either inhalation anesthesia or propofol infusion.

To diagnose hyperalgesia, the pain threshold was determined using a kit of 10 Von Frey monofilaments (VFM) calibrated to deliver an increasing force from 4 g (39.216 mN) to 300 g (2941.176 mN) (Touch-Test Sensory Evaluator, North Coast Medical, Inc., Morgan Hill, CA, USA) which were placed perpendicularly against the skin surface until they bent, for 1-1.5 s. An interval of 10 s was allowed between trials [30]. The assessment of acute pain and the quality of pain management was carried out by means of the Face, Legs, Activity, Cry, Consolability (FLACC) scale. The FLACC scale scores were determined at discharge in all children.

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 February 24, 2022.

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Results and Their Discussion

An analysis of group distribution revealed that the average age of children was 12.78±0.22 years, 11.29±0.29 years, and 11.8±0.11 years in Group I, Group II, and Group III, respectively. Body weight was found to be 39.03±1.44 kg, 37.28±2.99 kg, and 38.14±1.83 kg in Group I, Group II, and Group III, respectively. When assessing gender differences, a higher prevalence of the condition was observed in boys in all groups (Table 1).

Determination of the mechanical pain threshold around the postoperative wound in patients receiving intraoperative fentanyl infusion found that only 5 (15.1%) patients developed the response to the stimulus when applying pressure forces of 100 g and 180 g and the motor response to the stimulus intensity of 100 g.

The FLACC scale score was 3.1±0.2 points, indicating sufficient pain threshold. Twelve (36.4%) patients required pressure forces of either 26 g or 60 g and developed the motor response to the stimulus intensity of 26 g, with the FLACC scale score of 4.0±0.4 points, indicating insufficient pain threshold. Most (16, 48.5%) patients receiving fentanyl infusion developed the response to the stimulus only when applying pressure forces of 8 g and 10 g and the motor response to the stimulus intensity of 8 g, with the FLACC scale score of 5.1±0.3 points, indicating insufficient pain threshold and the risk of developing OIH in the early postoperative period. In patients receiving fentanyl at a dosage of 300-450 µg/day (10-15 µg/kg/day), the mean dose of fentanyl for adequate pain management was 10.2±0.4 µg/kg/hour (Table 2). When assessing the correlation using the Spearman’s correlation coefficient, a strong negative correlation was found between the daily fentanyl dose and the pressure force that elicited the stimulus (r = -0.69, p<0.05).

Table 1

Patient distribution by age, gender, and body weight

Indicator	Group I, n=33	Group II, n=27	Group III, n=27
	M±m	M±m	M±m
Age	12,78±0,22	11,29±0,29	11,8±0,11
Body weight	39,03±1,44	37,28±2,99	38,14±1,83
Boys, %	51,4±0,84	62,11±1,22	56,21±2,31
Girls, %	48,6±1,24	37,89±2,77	43,79±3,17

Table 2

Prevalence of hyperalgesia in patients undergoing surgery with various anesthesia techniques

Pressure force, g	Number of patients, abs./%	FLACC scale/ points	Daily fentanyl dose, µg/day	Mean fentanyl dose, µg/kg/day
Group I				
100-180	5 /15,1%	3,1±0,2	300	10.2±0.4*,**
26-60	12/36,4%	4,0± 0,4	350	
8-10	16/48,5%	5,1±0,3	450	
Group II				
100-180	14/52%	2,01±0,11	150	7,6±0,5
26-60	7 /26%	2,6±0,13*	200	
8-10	6 /22%	2,9±0,27*	250	
Group III				
100-180	18/67%	1,52±0,2**	100	4,2±1,4
26-60	6 /22 %	2,2±0,2**	150	
8-10	3 /11%	2,4±0,32**	200	

Notes:

- * a statistically significant difference between Group I and Group II (p<0.05)
- ** a statistically significant difference between Group I and Group III (p<0.05)

A study of the mechanical pain threshold in children after anterior abdominal wall surgery who received the TFPB by administering a solution of bupivacaine under ultrasound guidance and fractionated dose of fentanyl in the early postoperative period found an increase in the minimum mechanical pain threshold as compared to those receiving conventional anesthesia. It should be noted that determination of the mechanical pain threshold around the postoperative wound in patients receiving intraoperative fentanyl infusion and regional anesthesia found that most (14,

52%) patients developed the response to the stimulus when applying pressure forces of 100 g and 180 g and the motor response to the stimulus intensity of 100 g corresponded to the FLACC scale score, being on average 2.01±0.11 points, indicating sufficient pain threshold and adequate anesthesia. Seven (26%) patients required pressure forces of either 26 g or 60 g and the motor response to the stimulus intensity of 26 g corresponded to pain behavior on the FLACC scale, scoring 2.6±0.13 points, indicating sufficient pain threshold and adequate analgesic effect for

preventing hyperalgesia. In patients who received regional anesthesia, a reaction to stimulation when applying pressure forces of 8 g and 10 g was observed in 6 (22%) children, which was 2.6 times less compared to children who received conventional anesthesia. The motor response elicited by a stimulation force of 8 g and the FLACC scale score of 2.9 ± 0.27 points indicated sufficient pain threshold and a pronounced clinical effect of this anesthesia type for preventing hyperalgesia in the early postoperative period. The use of the TFPB allowed for a reduction in the fentanyl dosage (150-250 $\mu\text{g}/\text{day}$) to a maximum of 7-10 $\mu\text{g}/\text{kg}/\text{day}$, while the mean fentanyl dose for adequate pain management was 7.6 ± 0.5 $\mu\text{g}/\text{kg}/\text{hour}$, being 2.4 times less than in conventional anesthesia. A study of the mechanical pain threshold in children after anterior abdominal wall surgery who received the TFPB combined with the QLB (QLB+TFPB) by administering a solution of bupivacaine under ultrasound guidance and fractionated dose of fentanyl in the early postoperative period found an increase in the minimum mechanical pain threshold as compared to those receiving conventional anesthesia. It should be noted that determination of the mechanical pain threshold around the postoperative wound in patients receiving intraoperative fentanyl infusion and combined regional anesthesia found that most (18, 67%) patients developed the response to the stimulus when applying pressure forces of 100 g and 180 g and the motor response to the stimulus intensity of 100 g corresponded to pain behavior on the FLACC scale, scoring 1.52 ± 0.2 points, indicating sufficient pain threshold and adequate pain management. Six (22%) patients required pressure forces of either 26 g or 60 g and their motor response to the stimulus intensity of 26 g corresponded to pain behavior on the FLACC scale, scoring 2.2 ± 0.2 points, indicating sufficient pain threshold and adequate analgesic effect for preventing hyperalgesia. In patients who received combined regional anesthesia, a reaction to stimulation when applying pressure forces of 8 g and 10 g was observed only in 3 (11%) children. The motor response elicited by a stimulation force of 8 g and the FLACC scale score of 2.4 ± 0.32 points indicated sufficient pain threshold and a pronounced clinical effect of this anesthesia type for preventing hyperalgesia in the early postoperative period. The

use of combined regional anesthesia allowed for a reduction in the fentanyl dosage (100-20 $\mu\text{g}/\text{day}$) to a maximum of 3-5 $\mu\text{g}/\text{kg}/\text{day}$, while the mean fentanyl dose for adequate analgesia was 4.2 ± 1.4 $\mu\text{g}/\text{kg}/\text{hour}$, being 2.4 times less than in conventional anesthesia.

Postoperative anesthesia was conducted following the principles of multimodal analgesia. Children who received conventional opioid anesthesia were found to require greater doses of analgesics in the postoperative period (paracetamol injections – 366.93 ± 69.46 ml) as compared to those who received regional anesthesia (paracetamol injections – 366.93 ± 69.46 ml and 166.63 ± 20.05 ml in Group II and Group III, respectively, $p < 0.05$).

Conclusions

Thus, high fentanyl doses are associated with decreased pain threshold, which is likely related to the development of central OIH. The use of the TFPB alone and the combined regional nerve block, QLB+TFPB, by administering a solution of bupivacaine under ultrasound guidance reduces opioid use and pain sensations in children undergoing anterior abdominal wall surgery, prevents the development of hyperalgesia. The results obtained confirm the advantages of the combined regional nerve block over the nerve monoblock.

Prospects of further research

Further research on the impact of regional anesthesia techniques on hyperalgesia processes and triggers for the development of chronic postsurgical pain is promising.

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Conflict of Interests. The authors have no conflicts of interest to declare.

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Table 3

Postoperative pain management

Indicator	Group I, n=33	Group II, n=27	Group III, n=27
	M \pm M	M \pm M	M \pm M
Paracetamol, ml, IV	$366,93 \pm 69,46$	$209,38 \pm 47,12^*$	$166,63 \pm 20,05^{**}$

Notes:

* $p < 0.05$ - a statistically significant difference between Group I and Group II

** $p < 0.05$ - a statistically significant difference between Group I and Group III

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СПОСІБ ПРОФІЛАКТИКИ ГІПЕРАЛГЕЗІЇ У ДІТЕЙ ПРИ ВИКОРИСТАННІ РІЗНИХ МЕТОДИК ЗНЕБОЛЕННЯ

Я.В. Семкович¹, Д.В. Дмитрієв²

КНП «Івано-Франківська обласна дитяча клінічна лікарня Івано-Франківської обласної ради»
(м. Івано-Франківськ, Україна)¹

Вінницький національний медичний університет імені В.І. Пирогова
(м. Вінниця, Україна)²

Резюме

Вступ. Гіпералгезія, спричинена опіоїдами характеризується парадоксальною реакцією, за якої пацієнт, який отримує опіоїди для лікування болю, насправді може стати більш чутливим до певних больових подразників. Регіонарна анестезія також може впливати на центральну сенсibilізацію та зменшувати гіпералгезію після операції.

Метою дослідження було встановити спосіб профілактики гіпералгезії в ранньому післяопераційному періоді при різних схемах знеболення у дітей з операціями на передній черевній стінці.

Матеріал та методи дослідження. У дослідженні взяли участь 87 дітей віком 7-18 років, яким проводилось оперативне втручання на передній черевній стінці із різними варіантами анестезіологічного знеболення. І групу склали 33 дітей, оперованих на передній черевній стінці під загальним знеболенням із використанням фентанілу. ІІ групу склали 27 дітей, оперованих на передній черевній стінці, під загальним знеболенням із застосуванням регіонарного блоку поперечної фасції живота (TFPB). ІІІ групу склали 27 дітей, оперованих на передній черевній стінці, під загальним знеболенням із застосуванням регіонарного блоку поперечної фасції живота (TFPB) в поєднанні з блокадою квадратного м'яза попереку (QLB-4) із одного уколу.

Усі клінічні та лабораторні дослідження проводилися відповідно до Гельсінської декларації Всесвітньої медичної асоціації «Етичні принципи медичних досліджень за участю людини як об'єкт дослідження». Відповідно до чинного законодавства перед початком дослідження кожен його суб'єкт (батьки або повнолітні опікуни пацієнта) підписав детальну форму інформованої згоди на участь у дослідженні. Стаття пройшла комісію з питань етики на базі КНП «Івано-Франківська обласна дитяча клінічна лікарня ІФОР», що підтверджується витягом з протоколу комісії №2 від 24.02.2022 року.

Статистичну обробку отриманих даних проводили з застосуванням методів варіаційної статистики, кореляційного аналізу, критерію Стьюдента. Вірогідними вважались відмінності при $p < 0,05$. Порівняння часток здійснювалось за допомогою z-критерія.

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. В більшості пацієнтів І групи (48,5 %) реакція на подразнення виникала лише при застосуванні сили тиску 8 та 10 г, а рухова реакція була на подразнення з силою 8 г з оцінкою по шкалі FLACC $5,1 \pm 0,3$ бали, що свідчило про недостатній больовий поріг та можливий розвиток опіоїд-індукованої гіпералгезії в ранньому післяопераційному періоді. У пацієнтів ІІ та ІІІ груп реакція на подразнення з силою 8 г та оцінка по шкалі FLACC складала $2,9 \pm 0,27$ і $2,4 \pm 0,32$ балів відповідно ($p < 0,05$).

Висновки. Отримані результати підтверджують переваги застосування регіонарних методик знеболення в комплексі із традиційною аналгезією.

Ключові слова: гіпералгезія; діти; регіонарна аналгезія; міофасціальний блок.

Contact Information:

Yaroslav Semkovych – Candidate of Medical Science, Medical Director of Communal Non-Profit Enterprise “Ivano-Frankivsk Regional Children’s Clinical Hospital of Ivano-Frankivsk Regional Council”, Docent, Associate Professor, Department of Anesthesiology and Intensive Care of the Ivano-Frankivsk National Medical University (Ivano-Frankivsk, Ukraine).

e-mail: semkovych.doc@gmail.com

ORCID ID: <http://orcid.org/0000-0002-8319-022X>

Researcher ID: <https://www.researchrid.com/rid/AAY-7049-2020>

Scopus Author ID: <https://www.scopus.com/authid/detail.uri?authorId=57853725600>

Dmytro Dmytriiev – Doctor of Medical Science, Medical Director of Communal Non-Profit Enterprise “Podilskyi Regional Oncological Hospital of Vinnitsa Regional Council”, Professor, Department of Anesthesiology and Intensive Care of the Vinnitsa National Medical University (Vinnitsa, Ukraine).

e-mail: dmytrodmytriiev@gmail.com

ORCID ID: <https://orcid.org/0000-0001-6067-681X>

Researcher ID: <https://www.webofscience.com/wos/author/rid/M-6885-2016>

Scopus Author ID: <https://www.scopus.com/authid/detail.uri?authorId=57201489025>

Контактна інформація:

Семкович Ярослав Васильович – кандидат медичних наук, медичний директор КНП «Івано-Франківська обласна дитяча клінічна лікарня», доцент, доцент кафедри анестезіології та інтенсивної терапії Івано-Франківського національного медичного університету (м. Івано-Франківськ, Україна)

e-mail: semkovych.doc@gmail.com

ORCID ID: <http://orcid.org/0000-0002-8319-022X>

Researcher ID: <https://www.researchrid.com/rid/AAY-7049-2020>

Scopus Author ID: <https://www.scopus.com/authid/detail.uri?authorId=57853725600>

Дмитрієв Дмитро Валерійович – доктор медичних наук, медичний директор КНП «Подільський регіональний центр онкології», професор кафедри анестезіології, інтенсивної терапії та МНС Вінницького національного медичного університету ім. М.І Пирогова (м. Вінниця, Україна)

e-mail: dmytrodmytriiev@gmail.com

ORCID ID: <https://orcid.org/0000-0001-6067-681X>

Researcher ID: <https://www.webofscience.com/wos/author/rid/M-6885-2016>

Scopus Author ID: <https://www.scopus.com/authid/detail.uri?authorId=57201489025>



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