with the risk of the development of pathospermia will be established, this polymorphism can be considered as a new genetic factor of the prognosis for men with infertility (reproductive disorders). The obtained results indicate the effectiveness of study the *G-105A* polymorphism of *SEPS1* gene for the development of idiopathic infertility in men, for regarding reproductive potential for the patient and the selection of appropriate management.

Disclosures:
The authors declare no conflict of interest.

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UDC 616-053.3-009.7-089
DOI – https://doi.org/10.14300/mnnc.2018.13086
ISSN – 2073-8137

STUDY OF PAIN IN NEWBORNS

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ИССЛЕДОВАНИЕ БОЛИ У НОВОРОЖДЕННЫХ

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Evaluating the pain response in children is difficult. Nevertheless, the search for methods with which to assess pain objectively in newborns with surgical pathology of the digestive tract remains urgent. Therefore, we conducted a study of the serum concentrations of pain markers (substance P and neurokinin A) in infants to determine the relation of each of these

indicators to pain-intensity scales (COMFORT, VAS). This objective evaluation of pain in newborns allowed the provision of individualized care to these and other infants with necrotizing enterocolitis at various stages of the disease.

Keywords: pain, substance P, neurokinin A, COMFORT, VAS, NEC, newborns

Оценка болевой реакции у детей затруднительна, ввиду чего поиск методов объективной оценки болевого синдрома у новорожденных с хирургической патологией желудочно-кишечного тракта остаётся крайне актуальным. Проведено определение у 14 новорожденных сывороточной концентрации маркеров болевого синдрома (субстанции Р и нейрокинина А) с оценкой взаимосвязи данных показателей со шкалами интенсивности боли (COMFORT, VAS). Объективная оценка болевого синдрома у новорожденных позволила оказывать персонифицированную помощь при NEC на различных стадиях заболевания.

Ключевые слова: боль, вещество Р, нейрокинин А, шкала COMFORT, шкала ВАШ, НЭК, новорожденные

For citation: Obedin A. N., Kachanov A. V., Mashchenko A. N., Pozharsky V. P., Shmyreva E. S., Gerasimenko I. N., Filipieva N. V., Voronova A. A. STUDY OF PAIN IN NEWBORNS. *Medical News of North Caucasus*. 2018;13(3):490-492. DOI – https://doi.org/10.14300/mnnc.2018.13086

Для цитирования: Обедин А. Н., Качанов А. В., Мащенко А. Н., Пожарский В. П., Шмырева Е. С., Герасименко И. Н., Филипьева Н. В., Воронова А. А. ИССЛЕДОВАНИЕ БОЛИ У НОВОРОЖДЕННЫХ. *Медицинский вестник Северного Кавказа.* 2018;13(3):490-492. DOI – https://doi.org/10.14300/mnnc.2018.13086

COMFORT – behavioral scale reflecting pain
NEC – Necrotizing Enterocolitis
VAS – Visual Analogue Scale

Necrotizing enterocolitis (NEC) is one of the most common diseases in neonates that often requires surgery. It is associated with disability and a high mortality rate. The pain accompanying NEC at all stages of the pathological process is of an intense nature, making the course of the disease more difficult for both patient and physician [1]. The long-lasting pain leads to deterioration of physiological parameters in the newborn with NEC, activating a «stress response» and lengthening the recovery period [2, 3]. Methods to arrest the pain should correspond to the individual characteristics of the organism at fault, combining safety and effectiveness. Identifying a technique that could deliver an objective assessment of the pain could play an important role in achieving this goal because the currently available methods for assessing pain are mostly subjective [4].

The aim of this study was to evaluate the severity of pain in neonates with NEC by determining the serum concentrations of the neuropeptides responsible for transmitting pain impulses (substance P and neurokinin A) and clarify their relation to the results of pain-intensity scales (COMFORT, VAS).

Material and Methods. Altogether, we treated 14 neonates with NEC (8 boys, 6 girls) body weight 1378.5±104.3 g) in the anesthesiology and resuscitation intensive care units at Regional Children's Clinical Hospital and at the Stavropol Regional Clinical Perinatal Center № 1 (Stavropol) during 2016–2017. Among the 14 children, 6 (42.9 %) with NEC stages 1A–2A (group 1) were treated conservatively, and 8 (57.1 %) with NEC stages 2B–3B (group 2) underwent surgery. The comparison (control) group consisted of 20 children who had no intestinal wall pathology.

In addition to standard clinical indicators (heart rate, blood pressure) to assess the pain intensity in these neonates, we applied measurement scales [COMFORT (a behavioral scale for those who cannot express their pain severity) and a visual analogue scale (VAS)]. With the help of an enzyme-linked immunosorbent assay, the concentrations of substance P (Cloud-Clone Corp., Katy, TX, USA) and neurokinin A (RayBiotech, Norcross, GA, USA) of each patient were determined before starting treatment and on days 1 and 3 after treatment began. The statistical processing of the results of the research was carried out with the help of Excel 2010 (Microsoft, Edmond, WA, USA) and Statistica 10.0 (Statsoft, Topsfield, MA, USA)—programs that use variational statistics methods and estimate the reliability of differences in quantitative indicators (using Student's t test). The correlation between the indices was evaluated by Pearson's criterion (r).

Results and Discussion. Before starting treatment, in group 1 (conservative treatment), the substance P level was 427.4±87.1 pg/ml, and the neurokinin A level was 159.4±1.7 pg/ml. These pain markers in group 2 (surgery) were different from those in group 1. The substance P level was 425.0±138.7 pg/ml and the neurokinin A level was 18.36±3.7 pg/ml, which were significantly different from those in group 1, as well as those in the control group ($p<0.01$). Thus, both indicators were significantly lower in the controls (control levels: substance P 6.47±0.74 pg/ml, neurokinin A 6.29±0.5 pg/ml) than the corresponding data of either group 1 or group 2.

In addition, during the postoperative period, the dynamics of the indices of substance P in group 1 correlated with the severity of the pain as reflected in the assessment scales: COMFORT r=0.9 and VAS r=0.89. No correlations, however, were established between the neurokinin A concentration and the pain score on either the COMFORT scale (r=0.34) or VAS (0.38).

Group 1 newborns clearly showed a progressive decrease in the serum substance P level when the disease activity subsided clinically. The subsidence of the disease also corresponded with the subjective assessment of pain on the COMFORT scale: before treatment it was 11.7±0.3, at the end of day 1 of effective therapy it was 5.9±0.4, and by the end of day 3 it was 5.1±0.6. Undoubtedly, this trend is due to the subsidence of the inflammatory process and the effectiveness of analgesia with the use of regional techniques.

Thus, with a traditional analgesia regimen for NEC, we determined that at the end of postoperative day 1, group 2 children showed a decrease in substance P and neurokinin A levels (to 274.9±48.6 pg/ml and 12.3±0.8

pg/ml, respectively; $p<0.05$ for both). By the end of postoperative day 3, however, the substance P level had decreased (250.1±6.5 pg/ml). Similarly, the indicators reflecting the severity of the pain syndrome (COMFORT and VAS) were determined. Thus, by applying an individualized approach to each patient regarding regional analgesia, we could achieve stable, reliable pain relief for the patient.

It should be noted that, although currently there several scales for assessing pain, they are all subjective. The traditionally applied VAS scale is not applicable to newborns as it does not allow assessment of changes in their physiological status. At the same time, measuring neurotransmission in nerve fibers, facilitated by determining substance P and neurokinin A levels [2], can testify to the intensity of the pain. These tachykinin neuropeptides (algogenes) have functional properties that are similar to those isolated from the peripheral endings of C-fibers [5]. Nevertheless, a high degree of correlation of the level of the peptide substance P with the evaluation of recognized pain measurement standards (COMFORT and VAS scales) suggests that this particular peptide can serve as one of the options for objectively assessing pain, including in children.

Although the properties of neurokinin A have not been well studied [4], its interaction with NK-1 receptors could play an important role in the development of chronic pain syndrome. To objectify the assessment of acute pain syndrome, however, this neuropeptide is probably less suitable than substance P because there is no close relation between its level in the serum and the degree of pain according to known pain scales. When studying the characteristics of pain, such as in newborns, it is necessary to evaluate several indicators simultaneously. It is thus possible to obtain optimal measurements of pain in a group of newborns and premature infants with NEC by using a combination of behavioral (e.g., COMFORT scale) and physiological measurements, whereby we determine the intensity of the pain without verbal communication with the patient.

Conclusions. An objective measure of the pain response in newborns can be determined by measuring the serum concentrations of neuropeptides (substance P and neurokinin A). Substance P is a more sensitive marker because its concentration depends on the severity of acute pain and it is closely correlated with the level of pain scores (COMFORT and VAS). Neurokinin A is a less sensitive marker for assessing acute pain syndrome in newborns. Conducting an objective assessment of the severity of the pain syndrome allows us to individualize ongoing treatment in children with NEC.

Disclosures:
The authors declare no conflict of interest.

Acknowledgments. The work was supported by a grant from the President of the Russian Federation for young investigators MK-690.2017.7. We thank Nancy Schatken BS, MT(ASCP), from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

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