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Neuropathic pain as a predictor of neurological disorders regression in patients with spinal cord traumatic injury

For citation: Bol', sustavy, pozvonočnik. 2021;11(3):110-117. doi: 10.22141/2224-1507.11.3.2021.243047

Abstract. Background. Neuropathic pain is one of the principal secondary complications of spinal cord injury. The biological role of neuropathic pain has not been established yet. This type of pain is formed directly in the area of the spinal cord injury; therefore, it can be assumed that its intensity may characterize both degenerative and reparative processes. The aim of this work is to assess the possible relationship between the intensity of neuropathic pain in patients with spinal cord injury at cervical subaxial spine and the dynamics of neurological disorder regression. **Materials and methods.** We have performed a retrospective analysis of patients referred to outpatient department of the Romodanov Neurosurgery Institute of National Academy of Medical Sciences of Ukraine in the period from 2010 to 2020 after a surgical treatment of subaxial cervical spine traumatic injury. The extent of neurological disorders and the intensity of neuropathic pain were assessed within 5–7 and 11–13 months after surgery. **Results.** All 102 patients selected for analysis were divided into three groups depending on the intensity of the registered pain sensations: 1) absence of constant pain sensations — 19.6 % of subjects, 2) moderate pain — 56.9 %, 3) severe neuropathic pain — 23.5 %. In the first group, the regression of neurological disorders was 3.5 (95% confidence interval (CI) 2.15–6.15), in the second — 25.0 (95% CI 24.14–29.58), in the third — 13.0 (95% CI 10.87–16.55). The differences are statistically significant ($\chi^2 = 60.4$, $df = 2$, $p < 0.0001$). In patients with severe neurological disorders, the dynamics of recovery did not correlate with the pain intensity. With ASIA B, the dynamics of group 1 was 8.5 (95% CI 10.56–27.56), of group 2 — 15.0 (95% CI 13.41–18.41), of group 3 — 10.5 (95% CI 7.45–14.89). With ASIA C functional class, the difference is even more pronounced: in group 1, the median was 8.0 (95% CI 0.83–20.83), in group 2 — 32.0 (95% CI 25.41–36.86), in group 3 — 15.5 (95% CI 10.27–27.4). With ASIA D, a similar trend was observed. **Conclusions.** The worst regression of neurological disorders is observed in patients without clinically significant pain, the best results of neurological dysfunction recovery are found in patients with moderate neuropathic pain.

Keywords: spinal cord injury; subaxial level; neurological disorders; neuropathic pain; dynamics of recovery

Introduction

Spinal cord traumatic injury (SCTI) is one of the gravest consequences of traumatic impact on the human body; it involves the sensitivity and locomotor disorders, as well as autonomous dysfunctions of various intensity. One of the key secondary complications affecting not only the primary rehabilitation, but also the life quality at the later SCTI stages, is the pain [1, 2]. By the statistical assays, 65–85 % SCTI patients report the painful sensations; every one out of three patients register the occurrence of pronounced pains [3]. The pain may occur at the early stages, immediately after

trauma, or at the later stages [4]. The SCTI patients report both acute and chronic painful sensations [5]. Among the most prevalent pain types, the patients are subject to the nociceptive and neuropathic pain [6].

The nociceptive pain is the pain provoked by the irritation or injury of body tissues with no associated somatosensory disorders [7]. This type may be prevented by the etiotropic therapy, though more often it was chronic. With SCTI, there are three subtypes of nociceptive pain: 1) skeletal-muscular, 2) visceral, 3) other subtypes. The SCTI-attended skeletal-muscular pain occurs predominantly

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due to the mechanical injury of locomotor apparatus at the moment of injury, while the visceral pain is provoked by constipation. Another nociceptive pain may be caused by decubital ulcers [1].

According to the contemporary opinion, the nociceptive pain occurs due to a direct injury or disorder involving somatosensory system [8]. With SCTI, one distinguishes neuropathic pain at the injury level and below the injury level. This pain type is the most difficult to treat by medications, and along with spasticity it is one of the key factors determining the life quality of the sufferers [9].

It is evident that the nociceptive pain has a protective function, signaling the pathological focus existing at some location. The biological role of nociceptive pain is poorly explored. The clinical studies demonstrate that the intensity of neuropathic pain may vary to a large extent for the patients with a similar degree of injuries. Considering that this pain type is formed precisely at the site of spinal cord (SC) injury, one may suggest that the intensity of neuropathic pain, its dynamics, as well as the inclination to the pharmacological correction, are to some extent characterized by both degenerative and reparative processes occurring in SC. However, this issue is left unexplored.

The study **purpose** is to assess the probable correlation of neuropathic pain intensity suffered by patients after the spinal cord injury at the subaxial cervical spine level, and the dynamics of neurological disorder regression.

Materials and methods

Design of the study: retrospective observational study.

Participants of the study: in order to perform the study, one used the database of patients appealing for consultation to the polyclinical department of the SI Institute of Neurosurgery of the NAMS during the period of 2010-2020, after the surgical treatment of spinal cord traumatic injury at the subaxial level. The researchers have analyzed the findings of control examinations after 5-7 months and 11-13 months post-surgery. The patients were operated at the Institute of Neurosurgery of the NAMS, as well as at other treatment-prophylactic centers of Ukraine. All the patients gave their informed consents to process the treatment outcomes while keeping confidentiality. The study was approved by the Ethics and Bioethics Committee of the A.P. Romodanov Institute of Neurosurgery of the NAMS of Ukraine (protocol # 4 of 05.09.2018). This study is a fragment of research project (State registry number 0119U000110).

Inclusion criteria:

Traumatic injury of cervical spine at the subaxial level, which was attended by the neural injuries of spinal canal. Due to this fact, one performed surgical intervention of the necessary scope;

Patient age from 18 to 70 years;

Presence of closely documented characteristics of painful sensations;

Neurological deficiency at the moment of initial control examination is in line with A D functional class by the ASIA scale, though no higher than 250 points by the

International Standards for Neurological Classification of Spinal Cord Injury;

Presence of patient's informed consent.

Exclusion criteria:

Compression of spinal canal structures, kyphotic deformation of the operated spinal-locomotor segment, insufficient stability or other signs of ineffective surgical intervention;

Postoperative infectious-inflammatory complications;

Pre-injury neurological deficiency of any etiology and extent of pronouncement (due to the Traumatic Brain Injury (TBI), demyelinating process of central nervous system, peripheral nerve injury etc.);

Chronic painful sensations of any etiology requiring a regular use of medication before the injury;

History of trauma and/or surgery of spine or cervical area before the injuries analyzed in the study;

Historically and/or instrumentally confirmed inflammatory or clinically important degenerative-dystrophic changes of any spinal area before the injury;

Neoplastic process of any localization or any somatic pathology in decompensation;

Persistent mental and behavioral disorders.

Methods of clinical data evaluation. Basic demographic data: sex, age, mechanism of injury. The pre-surgery computer and magnetic resonance tomography determined the injury level and bone-traumatic changes by the AO *Spine subaxial cervical spine classification system* [10]. The functional class of neurological disorders was assessed by the ASIA (*American Spinal Injury Association*) scale. The detailed evaluation of neurological status was performed according to the ISNCSCI (*International Standards for Neurological Classification of Spinal Cord Injury*) [11, 12].

The registered painful sensations were characterized by the *International Spinal Cord Injury Pain (ISCIP) Classification* [6]. The intensity of painful sensations for each of the pain types was assessed by the *Numerical Rating Scale (NRS)*, where 0 stood for no pain, and 10 stood for the maximum possible pain [13].

Statistical processing. The findings were processed using R (version 4.0.5., *R Foundation for Statistical Computing*) in the *RStudio* (version 1.4.1106) environment. While analyzing the probability of statistical deviation Type 1 (α) was set at 0.05, the probability of statistical deviation Type 2 (β) was set at 0.2. The assessment of manifestation's correspondence to the normal distribution was performed using the Shapiro–Wilk test. In order to evaluate the character of distribution frequency, one used χ^2 criterion (Pearson correlation coefficient and Monte Carlo simulation method). The statistical significance of pain intensity distinction among groups was detected by means of Craskell–Wallace tests with Conover–Iman post-hoc test. The correction of comparative multitude was performed by *Yoav Benjamini* and *Yosef Hochberg*. The data were presented as median (95 % Confidence interval (CI)).

Results

General patients' characteristics

Upon analyzing the medical histories, one selected 163 patients corresponding to the criteria. After the further processing of data, 61 cases were excluded due to the following reasons: preserved compression of spinal canal ($n = 13$), grave kyphotic deformation of the operated spinal-locomotor segment ($n = 4$), post-operative infectious-inflammatory complications ($n = 3$), a history of Traumatic Brain Injury (TBI) ($n = 3$), chronic painful syndromes before the injury ($n = 11$), previous spinal surgeries ($n = 3$) or peripheral nerve surgeries ($n = 2$), a history of spondylodiscitis ($n = 2$), ankylosing spondyloarthritis ($n = 2$), present malignancy ($n = 4$), diabetes mellitus at the sub-compensation or decompensation stage ($n = 6$), a lack of clinical data ($n = 12$). Thus, in order to perform the further analysis one used the data of 102 patients (62.6 %). The general characteristics of the sample are presented in the Table 1.

Intensity of painful sensations

Considering the specific aim of the study involving the neuropathic pain intensity, one has divided the patients into three groups: 1 – no painful sensations (0-1 point by NRS), 2 – moderate pain (2-6 points), 3 – pronounced neuropathic pains (7-10 points). The data on patients' distribution as to the intensity of painful sensations 5-7 months after surgery are presented on Fig. 1. The distribution of this characteristic is statistically different from normal ($W = 0.95$, $p = 0.0015$) and is characterized by two peaks (in the first and second group of sufferers).

The absence of permanent painful sensations was observed in 19.6 % sufferers ($n = 20$), moderately painful sensations – in 56.9 % ($n = 58$), and intense painful sensations – in 23.5 % ($n = 24$).

It is quite understandable that all patients with painful sensations were regularly taking medications (predominantly Pregabalin or Gabapentin) in order to reduce the intensity of neuropathic pain. Moreover, the Group 2 actually includes patients with neuropathic pains removed by medications, while the Group 3 did not report any effectiveness of medications. The patients of Group 1 were taking medications to reduce the neuropathic pains either sporadically ($n = 8$) or not at all ($n = 12$).

The analysis into the painful sensation intensity among patients with various degrees of neurological disorders revealed certain regularities (Fig. 2). While exploring the sample 5-7 months after the surgery, the researchers detected significant differences in the patient distribution within the frameworks of each functional ASIA class ($\chi^2 = 37.088$, $p = 0.0005$). The most prominent distinctions as to the pain intensity were revealed among patients of ASIA's functional class A, while among the patients with ASIA's functional classes B, C and D one observed a similar tendency ($\chi^2 = 0.886$, $p = 0.939$).

In the group of patients with ASIA's functional class A, 83.3 % reported no neuropathic pain, while 16.7 % pointed out the painful sensations resistant to the specific medi-

cation use. In the group of patients with ASIA's functional class B, most cases (57.9 %) reported the neuropathic pain reducible by pharmacocorrection, while 31.6 % did not reveal any apparent efficacy of medication. 10.5 % did not report any pain at all. In the group of patients with ASIA's functional class C, most patients (62.5 %) reported a moderately intense pain with medication. Uncontrolled neuropathic pain intensity was detected in 25.0 % cases, no clinically significant painful sensations – in 12.5 %. In the group of sufferers with the least significant neurological disorders, 68.1 % reported a positive effect of medication, 21.2 % reported no effect, while 10.6 % cases reported absence of pain.

Overall, the tendency we've observed is in line with the previous studies and reference data. It is pointed out that the group of patients presenting a clinical picture of a full functional SC injury is the most heterogeneous out of all, since their symptoms may be attributed to both full anatomical SC injury and a grave contusion. Within ASIA's functional classes of B-D, the intensity of neurological disorders closely correlated with the degree of SC injury's severity, which accounts for a similar distribution in terms of neuropathic pain intensity. We did not assess the pain intensity in points within each functional class, which probably accounted for an absence of significant distinction among the functional classes of B, C and D. However, one observes a clear tendency of a growing number of cases with no painful sensations and intense pains associated with an increased degree of neurological disorders.

Table 1. Clinical characteristics of patients ($n = 102$)

Index	Value
Sex:	
Female	33 (32.4)
Male	69 (67.6)
Age, years:	
mean \pm standard deviation	41.09 \pm 16.10
median (range)	38.0 (18–69)
Circumstances attending the injury:	
Traffic accident	38 (37.3)
Diving	22 (21.3)
Fall from a height	27 (26.5)
Fall at the flat surface	10 (9.8)
Other	5 (4.9)
Level of injury:	
C3	5 (4.9)
C4	14 (13.7)
C5	31 (30.4)
C6	39 (38.2)
C7	13 (12.8)
Type of injury by AO Spine:	
A	59 (57.8)
B	23 (22.5)
C	20 (19.6)
Functional class by ASIA:	
A	12 (11.8)
B	19 (18.6)
C	24 (23.5)
D	47 (46.1)

Neurological deficiency regression

The dynamics of neurological disorder regression was assessed according to the difference between the total number of points by ISNCSCI, registered 5-7 and 11-13 months after surgery (Δ ISNCSCI). It was revealed that the neurological function recovery indices were to a great extent relying on the degree of initial neurological deficiency. Moreover, the minimal dynamics was observed among the patients grouped in ASIA's functional class A. 11-13 months after surgery, it was assessed as 0.5 (95 % CI: 0.12-2.12) points. 2 patients reported negative outcomes, probably attributed to the deviations. 4 patients reported no positive dynamics at all. The group of patients with ASIA's functional class B demonstrated an overall increase of this parameter by 13.0 (95 % CI: 11.5-15.76) points, while the group of patients with ASIA's functional class C – by 22.0 (95 % CI: 20.34-30.5) points. The greatest values were found among patients with the weakest neurological disorders (ASIA D) – 25.0 (95 % CI: 19.76-26.58) points. According to the rules of sample formation, the study did not involve patients with an overall number of points by ISNCSCI $>$ 250, since the weakest neurological disorders are regularly regressing irrespective of other factors, whenever there is a confirmed SCTI at the subaxial cervical spine. As the number of patients with various degrees of neurological disorders was disparate, one calculated the symptomatics' regressive variation coefficient. It was expected that the greatest values were obtained for the ASIA's functional class A (1.76), the fact attributed to the initial heterogeneity of the group.

The statistical processing of findings revealed statistically significant distinctions in terms of regression dynamics among patients of various functional classes ($\chi^2 = 41.47$, $df = 3$, $p < 0.0001$). The pairwise comparison detected a statistical significance of distinctions in all cases but for the ASIA C-ASIA D pair ($p = 0.19$), probably attributed to the sample structure.

While analyzing the neurological deficiency's regression in terms of neuropathic pain's intensity, one obtained the following data. The patients who had no clinically significant pain demonstrated an overall increase of neurological function up to 3.5 (95 % CI: 2.15-6.15) points, with neuropathic pain to be corrected by pharmacotherapy, while the regressing dysfunction median made 25.0 (95 % CI: 24.14-29.58) points with no effect from pharmacotherapy and intense pain present – 13.0 (95 % CI: 10.87-16.55) points. The distinctions are significant both for the total sample ($\chi^2 = 60.4$, $df = 2$, $p < 0.0001$) and for the pairwise comparison.

Due to the fact that the overall regression analysis was greatly determined by the initial level of disorders (see above), one has performed a detailed analysis (Fig. 3).

It was revealed that patients with grave neurological disorders had the recovery dynamics which did not correlate with the intensity of painful sensations. With no pain present (Group 1), the overall point difference by ISNCSCI made 0 (95 % CI -0.47–2.27) points, with intense pains resistant to medications (Group 3) – 1.5 (95 % CI -4.85–7.85) points. The Group 1 made of patients with

ASIA's functional class B had the dynamics of 8.5 (95 % CI -10.56–27.56) 5-7 months after surgery, the Group II (moderate pains alleviated by medications) had the dynamics of 15.0 (95 % CI 13.41–18.41), while the Group III had the dynamics of 10.5 (95 % CI 7.45–14.89) points. In the group of patients with ASIA's functional class C, the difference was even greater. Moreover, the Group I had a median of 8.0 (95 % CI -0.83–20.83) points, the Group II had a median of 32.0 (95 % CI 25.41–36.86), while the Group III had a median of 15.5 (95 % CI 10.27–27.4) points. The patients with the least pronounced neurological disorders revealed a similar picture: in the Group I Δ ISNCSCI made 5.0 (95 % CI 2.83–7.97) points, in the Group II – 29.0 (95 % CI 25.21–32.04), in the Group III – 13.0 (95 % CI 11.75-17.45) points. The assessment of statistical significance is presented in Table 2.

Discussion

According to the reference data, the functional recovery in the broadest sense of this word may be tentatively grouped into three dramatically different though inter-related mechanisms. This classification concerned those patients who suffered from SC traumatic injury, namely at the subaxial cervical spine level:

compensation involves the change of function, which may be achieved with no neurological deficiency changes (e.g. adaptation or new motion pattern formation, namely the improved self-care mechanisms unattended by the change of sensomotory function).

Neuroplasticity – mechanism determining reorganization of neuronal chains, e.g. during the motor training after the central nervous system injuries of either cortical or spinal level [14–16]. This type includes the functional improvements beyond the frameworks of neurological deficiency recovery, e.g. gait function improvement with no correspondent increase of muscle strength [17]. Furthermore, probably by means of neuroplasticity the segmentary injuries may recover.

The actual recovery mechanisms, such as remyelination or regeneration of injured spinal tract fibers, reflected in fact on the conductivity changes of spinal cord impulses and provoked the conductivity disorder decrease.

The neuropathic pain of patients with spinal cord injuries, both at the level of injury and below it, according to most researchers, is one of the neuroplasticity manifestations [18]. Back in 1978, M. Devor and P. D. Wall demonstrated that sensory axon injuries may provoke the changes in spinal cord sensory card organization [19]. One has later determined that decreased sensitivity, which is due to the neuropathic pain-associated sensitivity disorders, may be caused by the changes in the injured neuronal excitability and ectopic nervous pacemaker formation [20]. In the early 1980s, C. Woolf et al. suggested the central sensibilization theory describing the event cascade determining the non-adaptive neuroplastic changes of sensory structures and resulting in the neuropathic pain [21-23]. The studies revealed that collateral growth of small-diameter CGRP-immunoreactive primary afferent fibers in the III-V posterior horn after the SC injuries associated with

chronic neuropathic pain and autonomous dysreflexion [24]. The bigger-diameter fiber growth was also reported by N. R. Krenz and L. C. Weaver. This phenomenon may affect both the injury location (for instance, in case of neuropathic pain at the injury level or other SC sites (sensitivity disorders in the pelvic area with a high-level injury of thoracic region)). The described process promotes formation of myelinated afferent and non-myelinated C-fiber central sprouting, resulting in the initial sensory neuron hyperactivation and central inhibiting effect loss [25]. Despite a great number of experimental studies, the issue of whether neuropathic pain intensity of SCTI patients is a quantitative neuroplasticity criterion or whether neuropathic pain is a side effect with a negative clinical and pathophysiological role [18, 26-28].

It is worthy of note that a number of studies with various evidence base degree demonstrate that medications used to curb the intensity of neuropathic pain have a stimulating effect on the recovery of neurological functions in SCTI patients [29-31]. The mechanism of their immediate effect on the regeneration process is unexplored. J. J. Cragg et al. suggest that due to the diminished aberration plasticity and hyper-sensitivity, some medications used to treat the neuropathic pain after the SC injury may “retarget” or reveal the neurological recovery potential [32].

Having analyzed the reference data, we have detected individual studies of correlation between the neuropathic pain intensity and neurological disorder regression. The authors obtain inconclusive results, complicating the comparison and critical assessment of our data [32, 33].

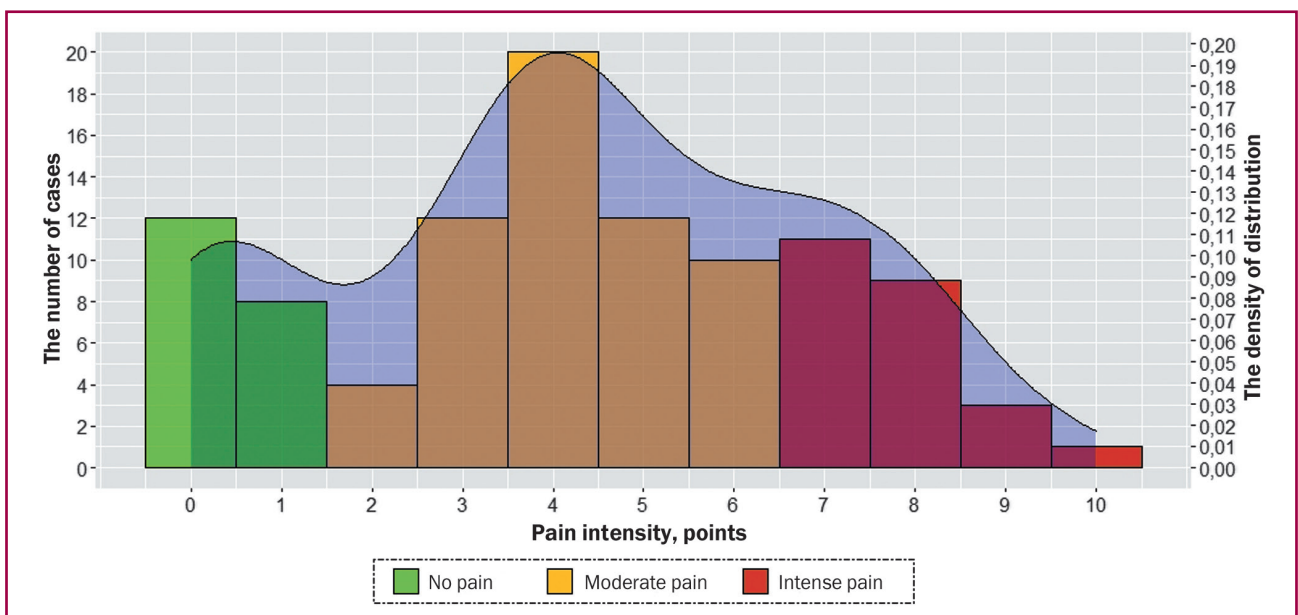


Figure 1. Distribution of patients with spinal cord injuries at the subaxial level of cervical spine 5-7 months after the surgery considering the neuropathic pain intensity.

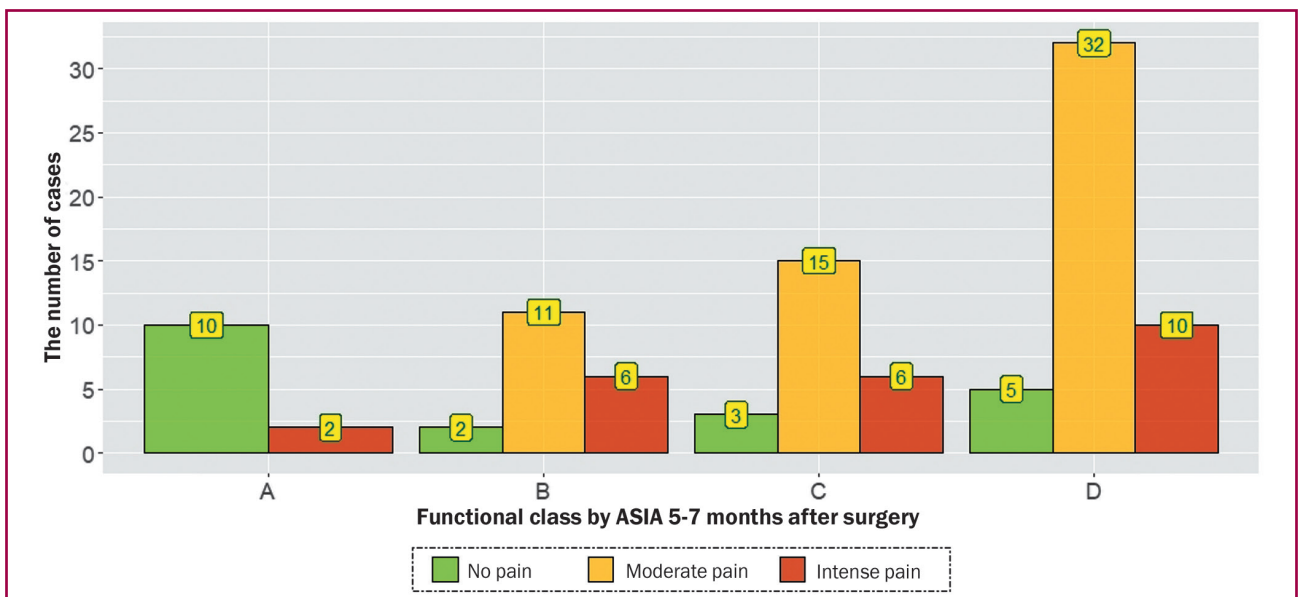


Figure 2. Distribution of patients with various degrees of neurological disorders in terms of neuropathic pain intensity.

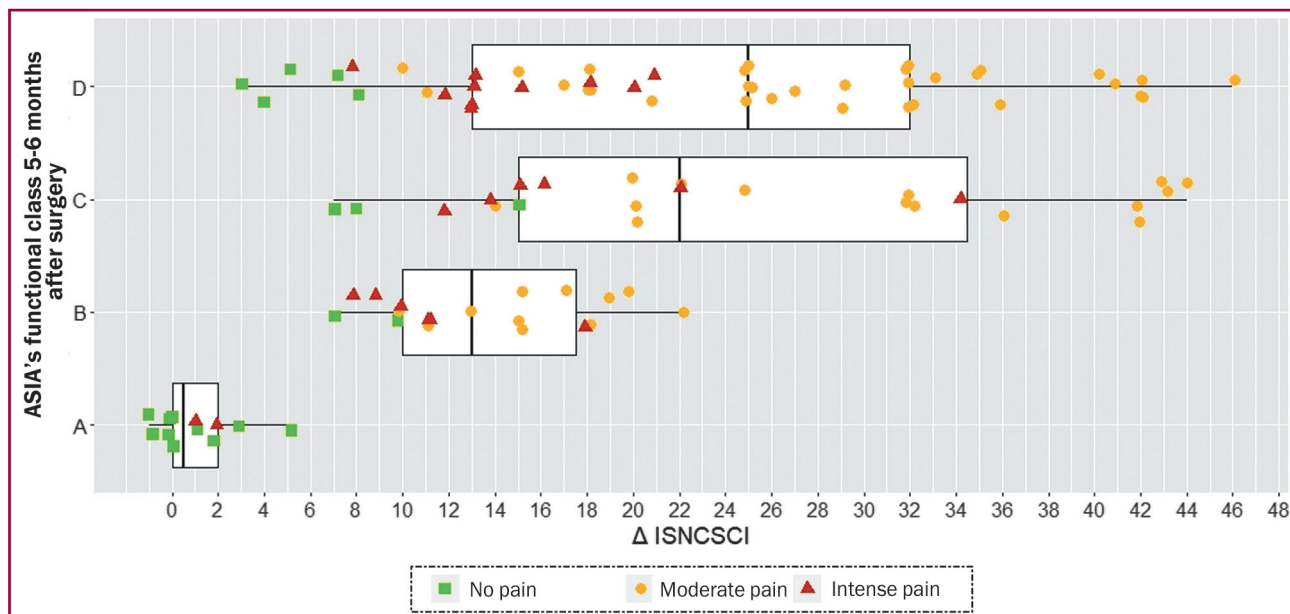


Figure 3. The neurological disorder regression dynamics among the patients with different ASIA functional classes and degree of neuropathic pain intensity

Table 2. Assessment of neurological disorder regression dynamics' statistical distinctions for patients with various degrees of neuropathic pain intensity within ASIA functional class

p**	Group of patients	
	I	II
ASIA's functional class A ($\chi^2 = 0.7736$; $df = 1$; $p=0.38$)*		
ASIA's functional class B ($\chi^2 = 8.0198$; $df = 2$; $p=0.02$)*		
Group of patients	II	0,0147
	III	0,1469
		0,012
ASIA's functional class C ($\chi^2 = 10.3731$; $df = 2$; $p=0.01$)*		
Group of patients	II	0,0021
	III	0,0817
		0,0102
ASIA's functional class D ($\chi^2 = 24.5151$; $df = 2$; $p<0.0001$)*		
Group of patients	II	< 0,0001
	III	0,0245
		< 0,0001

Notes: * — Craskell–Wallace tests; ** — Conover-Iman test with correction of comparative multitude performed by Yoav Benjamini and Yosef Hochberg method.

On the other hand, we have detected regularities in line with the above-mentioned pathophysiological pain formation and neuroplasticity aspects. They have a pivotal importance for the prognostication of SCTI outcomes and selection of optimal treatment tactics.

Conclusions

Our findings prove that the worst regression of neurological disorders is observed among the patients with clinically significant painful sensations, while the best values of neurological dysfunction recovery is registered among the patients with moderate neuropathic pains, which may be reduced by medications. The findings also suggest that the individual choice of adequate pharmacological therapy aimed at curbing the neuropathic pain for the spinal cord injuries has an important role to improve the overall

life quality, as well as to promote the spinal cord's functional recovery.

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Received 08.08.2021

Revised 20.08.2021

Accepted 31.08.2021 ■

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Information about funding. The work was performed as part of research project of Spinal Neurosurgery Department of the State Institution Romodanov Neurosurgery Institute of National Academy of Medical Sciences of Ukraine "Explore mechanisms and develop a complex of medical measures to reduce disability and improve the quality of life of patients with spine and spinal cord traumatic injury" state registration number 0119U000110.

Information on contribution of each author: Nekhlopochny Oleksii — concept and design of study, analysis of the data, text writing; Verbov Vadim — collection and processing of the material, text writing; Ia.V. Tsybaliuk — analysis of the data, text writing; Vorodi Milan — processing of the primary material, analysis of the data; Cheshuk Ievgen — processing of the primary material, analysis of the data.

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Нейропатичний біль як можливий предиктор регресу неврологічних розладів у пацієнтів із хребетно-спинномозковою травмою

Резюме. *Актуальність.* Нейропатичний біль є одним з основних вторинних ускладнень хребетно-спинномозкової травми. Біологічна роль нейропатичного болю не встановлена. Даний тип болю формується безпосередньо в зоні ураження спинного мозку, тому можна припустити, що його інтенсивність може характеризувати як дегенеративні, так і репаративні процеси. *Мета дослідження:* оцінити можливий взаємозв'язок між інтенсивністю нейропатичних больових відчуттів у пацієнтів, які перенесли хребетно-спинномозкову травму на субаксіальному рівні шийного відділу хребта, та динамікою регресу неврологічних розладів. *Матеріали та методи.* Проведений ретроспективний аналіз бази даних пацієнтів, які звернулися по консультативну допомогу в поліклінічне відділення Інституту нейрохірургії імені акад. А.П. Ромоданова НАМН України в період із 2010 по 2020 р. після хірургічного лікування травматичного пошкодження шийного відділу хребта на субаксіальному рівні. Оцінювали рівень неврологічних розладів та інтенсивність нейропатичного болю через 5–7 і 11–13 міс. після хірургічного втручання. *Результати.* Залежно від інтенсивності зареєстрованих больових відчуттів 102 пацієнти, які відібрані для аналізу, були розподілені на три групи: 1) із відсутністю постійних больових від-

чуттів — 19,6 % постраждалих, 2) помірним болям — 56,9 %, 3) вираженим нейропатичним болям — 23,5 %. У 1-й групі регрес неврологічних розладів становив 3,5 бала (95% довірчий інтервал (ДІ) 2,15–6,15), у 2-й — 25,0 (95% ДІ 24,14–29,58), у 3-й — 13,0 (95% ДІ 10,87–16,55). Відмінності статистично значущі ($\chi^2 = 60,4$, $p < 0,0001$). У пацієнтів із грубими неврологічними порушеннями динаміка відновлення не корелювала з інтенсивністю больових відчуттів. При ASIA B у 1-й групі динаміка становила 8,5 бала (95% ДІ 10,56–27,56), у 2-й групі — 15,0 (95% ДІ 13,41–18,41), у 3-й — 10,5 (95% ДІ 7,45–14,89). У пацієнтів із функціональним класом ASIA C різниця була ще вираженішою: у 1-й групі медіана становила 8,0 бала (95% ДІ 0,83–20,83), у 2-й — 32,0 (95% ДІ 25,41–36,86), у 3-й — 15,5 (95% ДІ 10,27–27,4). При ASIA D спостерігали схожу динаміку. *Висновки.* Найгірший регрес неврологічних порушень спостерігається в пацієнтів без клінічно значимих больових відчуттів, найкращі показники відновлення неврологічної дисфункції — у пацієнтів із помірними нейропатичними болями.

Ключові слова: хребетно-спинномозкова травма; субаксіальний рівень; неврологічні розлади; нейропатичний біль; динаміка відновлення