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LOSS OF TEMPERATURE AND PAIN SENSATION AS RISK MARKER OF NEUROLOGICAL COMPLICATIONS IN SURGICAL CORRECTION OF SEVERE SPINAL DEFORMITY

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Background. Treatment of severe spinal deformity remains a challenging surgical problem, with an iatrogenic injury to the spinal cord being a critical complication. There is a high risk of neurological deficit following surgical correction of a severe spinal deformity.

Aim. To determine the relationship between the extent of disturbed thermal and pain sensations at Th_1-S_2 dermatomas and the intensity of the spinal cord pathways' responses to surgical correction of the severe spinal deformity.

Material and methods. We reviewed 58 patients with severe spinal deformities of different etiologies (mean age, 15.7±0.8 years). All patients underwent surgical deformity correction followed by thoracic/thoracolumbar spine fixation by using a variety of internal transpedicular fixations. Intraoperative neurophysiological monitoring (IONM) with transcranial motor-evoked potentials (MEPs) was used during operative interventions. Preoperative and postoperative thermal and pain sensations were assessed in Th_1-S_2 dermatomas to the right and left by using an electrical aesthesiometer.

Results. The extent of disturbed preoperative and postoperative thermal and pain sensations in Th_1-S_2 dermatomas before and after correction of spinal deformities correlated with the response type scale (I–V) of the spinal cord pathways to the surgical correction we offered. Correlation between the response type and characteristics of thermal and pain sensations was mostly revealed by the test results for the thermal pain threshold (thermal analgesia). The incidence of postoperative thermal analgesia increased monotonically from patients with response type I (persistent MEP form and amplitude-time parameters close to the baseline) to patients with response type V (higher risk of neurological complications). The overall rate of thermal analgesia increased after surgical correction of the spinal deformity relative to the baseline and was higher (≤8%) in patients with response type V.

Conclusions. Surgeons and neurophysiologists who perform IONM should give careful attention to patients with severe spinal deformity who exhibit marked postoperative thermal analgesia.

Keywords: severe spinal deformity; spinal deformity correction; intraoperative neurophysiological monitoring (IONM); transcranial motor-evoked potentials (MEP); temperature and pain sensation; thermal analgesia.

СОСТОЯНИЕ ТЕМПЕРАТУРНО-БОЛЕВОЙ ЧУВСТВИТЕЛЬНОСТИ — МАРКЕР УРОВНЯ РИСКА НЕВРОЛОГИЧЕСКИХ ОСЛОЖНЕНИЙ ПРИ ХИРУРГИЧЕСКОЙ КОРРЕКЦИИ ТЯЖЕЛЫХ ДЕФОРМАЦИЙ ПОЗВОНОЧНИКА

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Актуальность. Лечение тяжелых деформаций позвоночника представляет собой серьезную хирургическую проблему. При этом ятрогенная травма спинного мозга остается опасным осложнением. Существует повышенный риск неврологических дефицитов после операции коррекции тяжелой деформации позвоночника.

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Цель исследования — определение характера взаимосвязи между степенью нарушения температурно-болевой чувствительности в области дерматомов Th_1-S_2 и интенсивностью реакции проводящих путей спинного мозга на хирургическую коррекцию тяжелых деформаций позвоночника.

Материалы и методы. Работа основана на результатах исследования 58 больных с тяжелыми деформациями позвоночника разной этиологии (средний возраст — 15,7 ± 0,8 года). Всем пациентам была произведена коррекция деформации с последующей фиксацией сегментов грудного/грудопоясничного отдела позвоночника с использованием различных вариантов погружных систем транспедикулярной фиксации. Оперативное вмешательство осуществлялось под интраоперационным нейрофизиологическим мониторингом (ИОНМ) с применением моторных транскраниально вызванных потенциалов (МВП). Температурно-болевая чувствительность оценивалась с помощью электрического эстезиометра в дерматомах Th_1-S_2 справа и слева до и после хирургического лечения.

Результаты. Степень нарушения температурно-болевой чувствительности в области дерматомов Th_1-S_2 до и после оперативной коррекции деформации позвоночника коррелирует с предложенной нами шкалой типов реакций (I–V) проводящих путей спинного мозга на хирургическую агрессию. Связь типа реакции с характеристиками температурно-болевой чувствительности в большей степени проявляется для результатов тестирования порогов боли от горячего (термоаналгезии). Частота встречаемости термоаналгезии в предоперационном периоде монотонно возрастает от группы пациентов с первым типом реакции (сохранение на момент тестирования формы и амплитудно-временных параметров МВП, близкими к исходным) к группе больных с пятым типом (высокий риск неврологических осложнений). После оперативной коррекции деформации позвоночника общая частота термоаналгезии повышается по сравнению с исходным уровнем, но в большей степени (до 8 %) термоаналгезия регистрируется в группе больных с пятым типом реакции.

Заключение. Определение в предоперационном периоде у больных с тяжелыми деформациями позвоночника значительной выраженности термоаналгезии может рассматриваться как признак, требующий повышенного внимания со стороны хирурга и нейрофизиолога, проводящего ИОНМ.

Ключевые слова: тяжелые деформации позвоночника; коррекция деформации позвоночника; интраоперационный нейрофизиологический мониторинг (ИОНМ); моторные транскраниально вызванные потенциалы (МВП); температурно-болевая чувствительность; термоаналгезия.

Introduction

Treatment of severe spine deformities is a serious surgical problem [1–5], and iatrogenic spinal cord injury remains a dangerous complication. Previous studies have shown that the frequency of postoperative neurologic complications ranges from 0.37% to 10% [6–10]. Intraoperative neurophysiological monitoring (IONM) of the spinal tracts is used as a preventive measure [5].

Transcranial motor evoked potentials (MEPs) are extremely sensitive to changes in blood flow in the spinal cord due to hypotension or compression (lesions) of the blood vessels [8, 9] and currently are an important component of the IONM gold standard for the correction of spinal deformities [8, 11–15]. Changes in MEP parameters in response to surgical aggression are often detected sooner than the changes in somatosensory evoked potentials, which facilitate faster identification of an impending spinal cord injury [8]. However, some researchers believe there is insufficient evidence about IONM reducing the incidence of a new or the exacerbation of an existing sensorimotor deficiency [16, 17]. IONM tools cannot differentiate changes in the control parameters associated with the surgeon's actions and the reactions caused by general transformation of the functional state of the central nervous system [12, 18]. In this regard, further prospective studies are required.

Study of thermal and pain sensitivity in Th_1–S_2 dermatomes in patients with severe spinal deformities allows assessing the integrity of the skin's sensory system's functions and its compensatory adaptive capabilities in the correction of spinal deformities. Our study aimed to determine the correlation between the degree of defects of the thermal and pain sensitivity in the Th_1–S_2 dermatomes and the intensity of the spinal tracts' reaction to surgical correction of severe spinal deformities.

Materials and methods

Our study sample included 58 patients (24 males and 34 females) aged 2.9–27 years (15.7 ± 0.8 years), with severe spinal deformities.

The causes of deformity were idiopathic scoliosis in 26 cases, congenital scoliosis in 22 cases, type I neurofibromatosis in four cases, neuromuscular scoliosis in three cases, and other factors (such as neoplasms) in three cases. The average angle of deformity of the primary curve was 80.1° ± 7.1° (range, 50°–145°), whereas that of the secondary curve was 51.8° ± 9.4° (range, 20°–135°).

Deformities of all patients were corrected under the IONM control (63 protocols), followed by fixation of segments of the thoracic/thoracolumbar spine using different immersible transpedicular fixation systems [19–22]. The following procedures were performed: seven osteotomies, five vertebrotomies, three extirpations of the semivertebra, release, and discotomy.

Anesthetic support combined (i) intravenous anesthesia as a combination of a hypnotic, propofol (10^{-2} mg/kg/h), with a narcotic-analgesic, fentanyl (10^{-1} μg/kg/h), (ii) an intravenous microfluid injection through an infusion pump, and (iii) artificial lung ventilation through an endotracheal tube. During intubation, esmeron, a muscle relaxant of average action, was used. The surgery duration averaged 235.0 ± 13.5 min (range, 60–470 min), and intraoperative blood loss amounted to 556.0 ± 51.4 mL (range, 100–1500 mL).

The study was approved by the Ethics Committee of the Federal State Budgetary Institution, Ilizarov Russian Research Center of Restorative Traumatology and Orthopedics, Ministry of Health of Russia (Minutes No 7 [32] of 12.24.2012). It was conducted in compliance with the ethical standards set forth in the World Medical Association's "WMA Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects" (as revised in 2013). Patients aged ≥18 years as well as parents or legal guardians of pediatric patients signed informed consent for diagnostic studies and publication of the data without personal identification.

Thermal and pain sensitivities were tested before and after 2–3 weeks of surgery (depending on each patient's condition) with an electrical esthesiometer (a thermistor, EPCOS Inc., Germany) with simultaneous skin temperature registration (Termostar, Nihon Kohden, Japan). To test the thermal and pain sensitivities, we evaluated the temperature perception in response to local heating of the skin in the selected dermatome region. Temperature sensations were divided into two categories: (i) "thermal" and (ii) "pain from heat." The contact area of the thermoelectric couple was 1 cm^2, the temperature ranged from 10°C to 50°C, and the rate of temperature increase was 2°C/min. Assessment of thermal and pain sensitivities was performed in accordance with the generally accepted scheme [23] at symmetrical points on the right and left of Th_1–S_2 dermatomes.

Conformity to normal statistical distribution of the thresholds values of thermal and pain sensitivities from heat was estimated using the Kolmogorov and Smirnov criteria. Their arithmetic mean (M) and the standard error of mean (m) as well as the occurrence frequency (ν) of lack of thermal (thermoanesthesia) and lack of pain (thermoanalgesia) sensation as a percentage ratio of the number of observations for thermoanesthesia (n_1) and thermoanalgesia (n_2), respectively, to the total number of observations in the analyzed sample (N) were calculated:

$$\nu_i = \frac{n_i \cdot 100\%}{N}. \quad (1)$$

where n_i is the number of observations of the i-th parameter.

The error (S_ν) was calculated from the occurrence frequency as

$$S_\nu = \sqrt{\frac{\nu(1-\nu)}{N}}, \quad (2)$$

The statistical significance of the differences in the esthesiometric parameters between the compared groups with normal distribution was assessed using Student's t-test ($p < 0.05$). For a small sample, a nonparametric Mann–Whitney U-test was used ($p < 0.05$). The significance of changes in the occurrence frequency of thermoanesthesia and thermoanalgesia was evaluated using the z-test of the difference in proportions. The data obtained were mathematically processed using Microsoft Excel 2010 with the Attestat add-on [24].

IONM was performed using the ISIS IOM system (Inomed Medizintechnik GmbH, Germany). We have described its implementation scheme in detail in a previous study [25]. The reactions of MEPs registered during monitoring were ranked according to the scale we previously developed [25] from 0 (preservation at the time of testing of the form, amplitude, and time parameters of MEPs close to initial ones) to 7 (complete disappearance of MEPs without signs of restoration by the time of surgery completion). During subsequent testing, the rank estimate was either maintained at the same level (relative to previous MEP dynamics) or increased or decreased depending on the ability of the somatic motor system to transmit the excitation wave from the motor cortex to the muscle indicator. The changes in MEP rankings during surgery characterized the reaction type of the somatic motor system to surgery. We identified five stable combinations of ranks corresponding to five types of spinal tract reactions to surgical aggression [25]. The occurrence frequency was calculated by equation (1), and its error was calculated by equation (2) for each type of reaction identified.

Results

Analysis of the thermal and pain sensitivity parameters determined that the preoperative average values of thresholds of thermal (Figure 1*a*) and pain (Figure 1*b*) sensitivity (at symmetrical right and left test points) were similar ($p > 0.05$) and increased unidirectionally with insignificant variation in the caudal direction (from the Th_1 dermatome to the S_2 dermatome).

Comparing the sensitivity thresholds in patients with normal values (Figure 1) revealed that the thermal sensitivity threshold in the Th_3 dermatome increased by 2°C–7°C (average 5.3°C ± 1.2°C, $p < 0.05$) and that the pain sensitivity in the Th_5–Th_6 dermatomes increased by 2°C–8°C (average 4.3°C ± 0.7°C, $p < 0.05$).

The occurrence frequency of thermoanesthesia and thermoanalgesia is presented in Figure 2. The preoperative bilateral differences of this indicator were, as a rule, insignificant. Thermoanesthesia (Figure 2*a*) was more pronounced (before treatment 27%–56%, after treatment 22%–58%) than thermoanalgesia (before treatment 0%–2%, after treatment 0%–8%) (Figure 2*b*). The distribution of thermoanesthesia was more or less even across all tested dermatomes, with a slight tendency to increase in the caudal direction, whereas that of thermoanalgesia was uneven and occurred randomly (Figure 2*b*).

Before surgery, but after anesthetic induction and the offset of action of the muscle relaxant, baseline MEPs were obtained to assess the degree

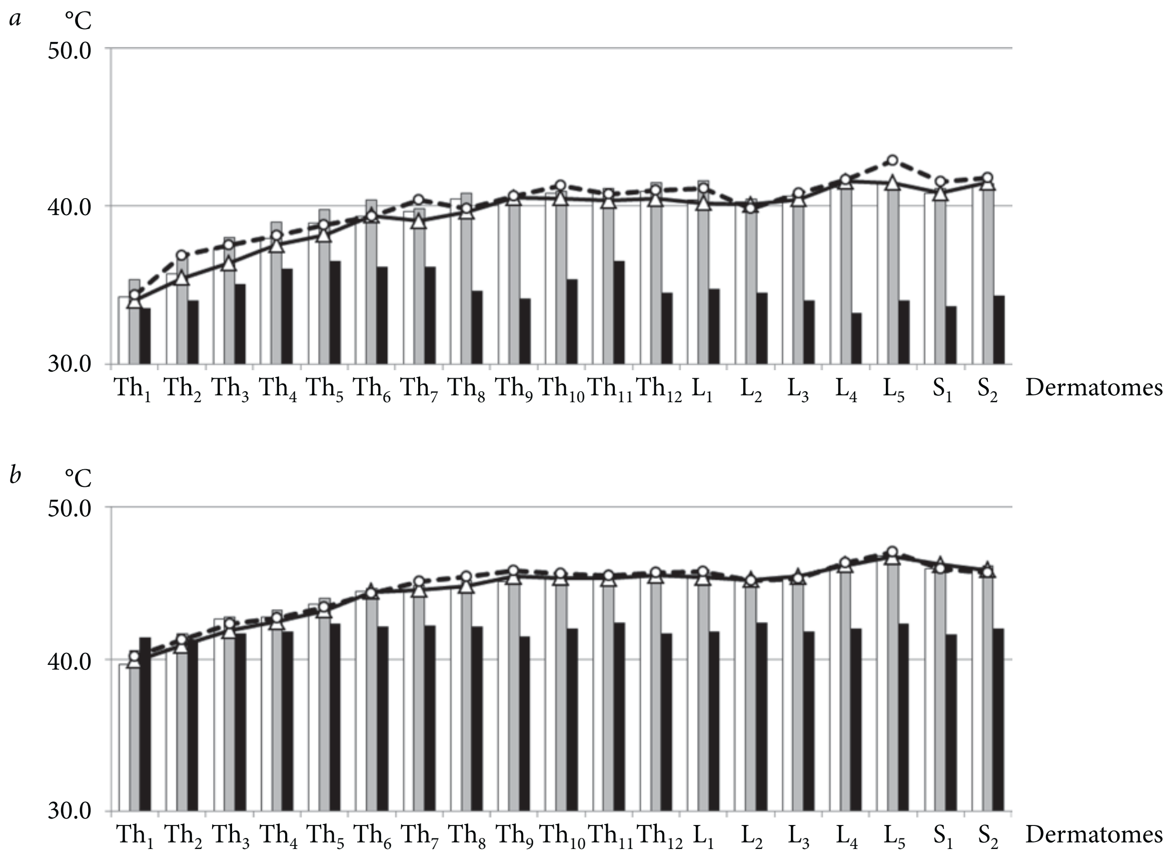

Fig. 1. Thresholds of (*a*) thermal sensitivity and (*b*) pain sensitivity in Th_1–S_2 dermatomes before treatment (columns: white — the right test points; gray — the left test points) and after treatment (lines: solid — the right test points; dashed — the left test points). Black columns are normal threshold values

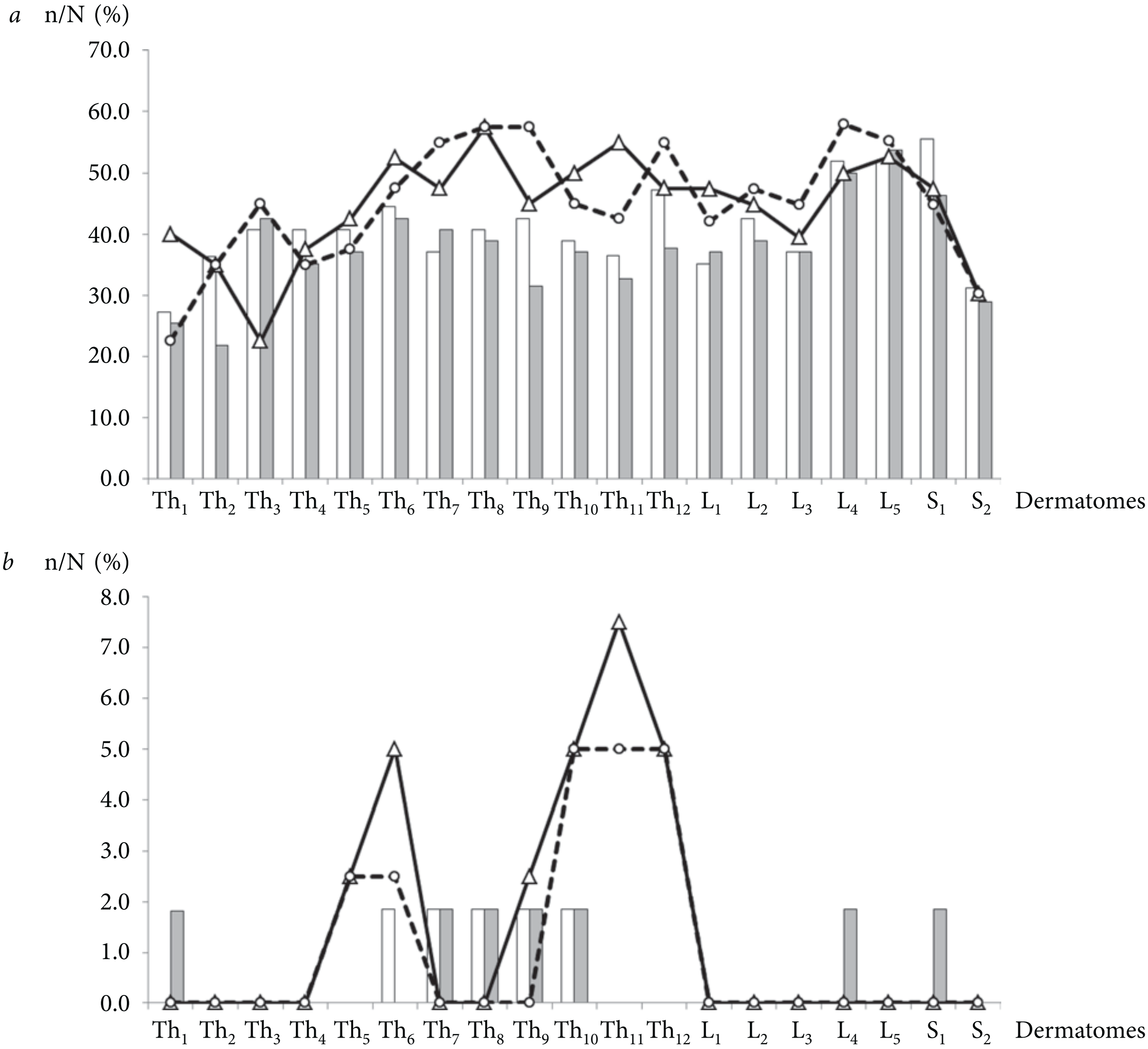

Fig. 2. Occurrence frequency of (*a*) thermoanesthesia and (*b*) thermoanalgesia before treatment (columns: white — the right test points; gray — the left test points) and after treatment (lines: solid — the right test points; dashed — the left test points)

of change in the control responses during surgery. In three cases, the initial responses showed unstable shapes and characteristics; in two cases, basic MEPs could not be obtained; and in one case, they were observed only in the leads on the left and had low amplitude.

During surgery, practically all variants of MEP changes were observed relative to the baseline: from a moderate decrease and instability in shape and characteristics to a significant decrease until complete disappearance. By analyzing the IONM protocols, all indicated variants of MEP changes were categorized into the five stable combinations of ranks identified earlier, the frequency of which is presented in Table 1.

Table 1 shows that the use of MEP technology for surgical correction of spinal deformities is accompanied by a low risk of developing neurological complications. When reaction types IV and V were identified, due to timely measures (transposition of screws, administration of glucocorticoids, partial discharge of traction loads to the spinal cord), in most cases, the motor functions of patients remained at a level corresponding to the preoperative level. In one case (of six cases), after having a type V reaction, the patient underwent repeated surgery (discharge of traction loads). In three cases (4.8%), there were electromyography (EMG) signs of spinal cord root irrigation, such as short-term outbreaks of spontaneous EMG in the corresponding leads, which subsided as a result of corrective action by the surgeons.

Postoperative control esthesiometric examination showed that compared with the

Table 1

Reaction types (I–V) of the spinal tracts to surgical correction of spinal deformities

Type	Combinations of ranks	Number of observations	Occurrence frequency (ν), %	Risk of neurologic complications
I	0, 1, 2	28	44.4 ± 6.26	Absence of risk
II	0–3, 4a	8	12.7 ± 4.19	Minimum risk
III	0–3, 4a, 5	11	17.5 ± 4.60	Low risk
IV	0–3, 4b, 5, 6	10	15.9 ± 4.60	Average risk
V	0–3, 4b, 5, 6, 7	6	9.5 ± 4.00	High risk

Note: The occurrence frequency was calculated by equation (1) without taking into account two observations with an initial lack of response ($N = 63 - 2$), and its error ($S_ν$) was calculated by equation (2).

baseline, changes in the average thermal and pain sensitivity thresholds (Figure 1) vary insignificantly ($p > 0.05$). The nature of their distribution along the spine and the degree of bilateral differences ($p > 0.05$) were retained. The postoperative occurrence frequency of thermoanesthesia varies ambiguously (Figure 2*a*). In the upper thoracic region, these changes are multidirectional. For the Th_3 dermatome, the decrease in this parameter is statistically significant on the left ($p < 0.05$). Starting from the Th_6 dermatome, there is a distinct increase in the postoperative occurrence frequency of thermoanesthesia compared with the baseline. In the lumbar region, changes in this parameter can be considered insignificant. Figure 2*b* shows that the manifestations of thermoanalgesia are more uneven than the local loss of thermal sensation; however, after surgery, the occurrence frequency of thermoanalgesia in the analyzed sample increases significantly in the lower part of the thoracic spine, as in the case of thermoanesthesia.

The entire patient sample was divided into four groups (Figure 3), depending on the type of reaction of the spinal tracts to surgery.

Group 1 (Figure 3*a*) included patients who did not show changes in MEPs during surgery (reaction type I). Group 2 (Figure 3*b*) comprised patients with reversible changes in MEPs during surgery (reaction types II and III). Group 3 (Figure 3*c*) included patients with reaction type IV; their MEP range decreased to the critical level and remained the same after surgery. Group 4 (Figure 3*d*) patients showed long-term disappearance of MEPs during surgery. Postoperative examination of patients with reaction types I–IV showed that changes in the mean values of thermal and pain sensitivity thresholds were statistically insignificant compared with the baseline ($p > 0.05$); for reaction type V (group 4), the small sample size and high variability (much higher than other reaction types) did not enable us to reliably estimate the significance of changes in thermal sensitivity thresholds after surgery. Moreover, the thresholds of pain sensitivity due to heat changed unreliably.

Due to the small sample size of groups 3 and 4, comparing the occurrence frequencies of thermoanesthesia and thermoanalgesia, depending on the reaction type of the spinal tracts to surgical aggression for each dermatome, was not helpful because it was for the entire sample (Figure 2). The preoperative occurrence frequency of thermoanesthesia (Figure 4*a*) varied significantly in the compared groups; the intergroup differences were most likely random, but they showed a slight tendency to increase in patients with reaction type V compared with those with reaction type I. The overall postoperative occurrence frequency of thermoanesthesia was 14.3% higher ($p < 0.05$) than that before surgery. In three groups of four patients, it increased by 44.5% (type I), 23.6% (type IV), and 30.3% (type V) ($p < 0.05$) compared with the baseline. This increase was the most pronounced in patients with reaction type V and was the highest at 68% after surgery.

The preoperative occurrence frequency of thermoanalgesia (Figure 4*b*) varied significantly in the compared groups. Although intergroup differences were most likely random, there was a slight tendency to increase from reaction type I (0% in the absence of thermoanalgesia, 28 patients, 532 dermatomes, 1064 measurements) to

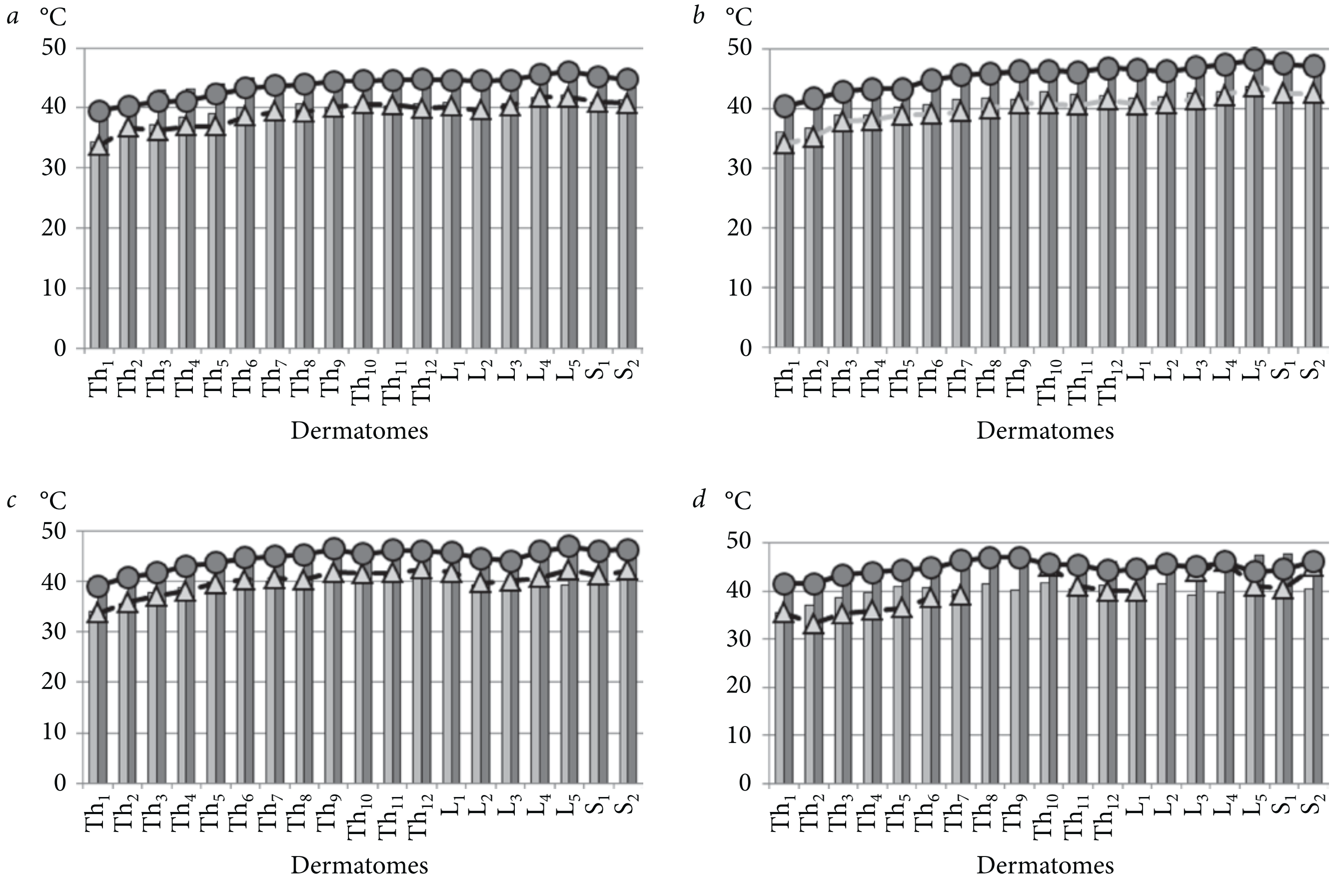

Fig. 3. Thresholds of thermal and pain sensitivity before treatment (columns: light gray, thermal threshold; dark gray, pain threshold) and after treatment (lines: dashed, thermal threshold; solid, pain threshold) for different reaction types of the spinal tracts to surgery. (*a*) Group 1 (type I), (*b*) group 2 (types II and III), (*c*) group 3 (type IV), and (*d*) group 4 (type V)

reaction type V (4.3%, 6 patients, 114 dermatomes, 228 measurements).

The overall postoperative occurrence frequency of thermoanalgesia was 160% higher ($p \leq 0.05$) than that before surgery. In three groups of four patients, it increased compared with the baseline: in group 1, thermoanalgesia appeared in 0.5% of dermatomes; in group 2, it increased by 4.5 times; and in group 4, it increased by 86% ($p \leq 0.05$). This increase was the most pronounced for patients with reaction type V and was the highest at 8% after surgery.

The preoperative occurrence frequency of thermoanalgesia increased monotonically from patients with reaction type I to those with reaction type V. After surgical correction of spinal deformities, the total frequency $\nu(T_2)$ increased compared with the baseline. In this case, the intergroup differences among patients with reaction type I–IV (groups 1–3) were less pronounced compared with patients with reaction type V (group 4). Patients with reaction types IV and V (groups 3 and 4) (Table 2), on average, did not significantly differ from patients with reaction types I–III (groups 1 and 2) in age, magnitude of deformity of the primary curve, degree of deformity correction, and intraoperative blood loss volume.

The proportion of patients with congenital scoliosis and kyphotic deformity, who underwent osteotomy, was greater in groups 1 and 2 (reaction types I–III). In group 4 (reaction type V), there were no patients with kyphotic deformity, and osteotomy was not performed. From the entire sample of patients, only one patient (group 3, reaction type IV) had an intraoperative complication associated with unstable hemodynamics and blood loss. The percentage of patients with neurological disorders before surgery was greater in groups 3 and 4 (reaction types IV and V) than in groups 1 and 2 (reaction types I–III).

The results showed that changes in the state of thermal and pain sensitivities of patients before and after surgical correction of spinal deformities correspond to the proposed scale of the reaction types of the spinal tracts to surgery. This relationship

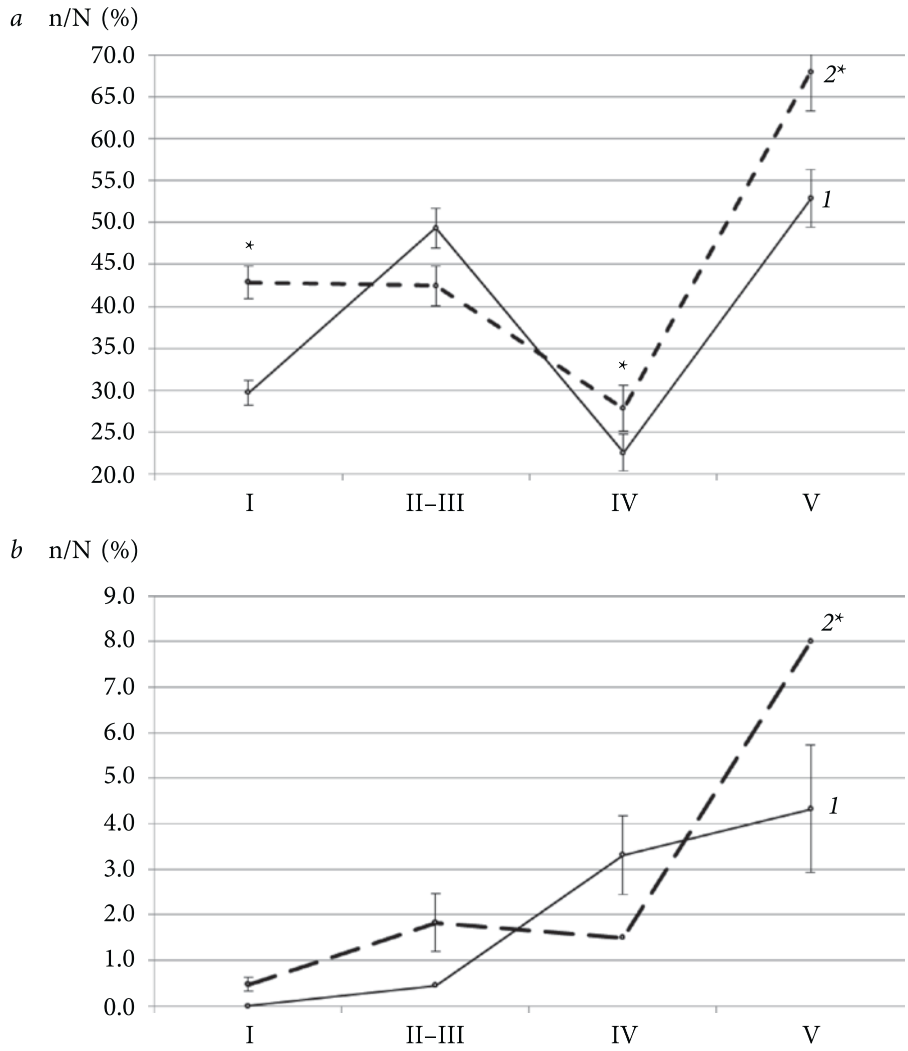

Fig. 4. Frequency distribution of (*a*) thermoanesthesia and (*b*) thermoanalgesia (1) before and (2) after surgery, depending on the type of reaction of the spinal tracts. *reliability of the difference between the indicators and preoperative level, $p < 0.05$

Table 2

Characteristics of patients with different reaction types (I–V) of spinal tracts to surgical correction of spinal deformities

Indicators	Reaction types of spinal tracts		
	Types I, II, and III (n = 47)	Type IV (n = 10)	Type V (n = 6)
Age, years	15.3 ± 0.9	19.1 ± 2.1	14.2 ± 1.7
Magnitude of deformity of the primary curve, °	78.4 ± 4.1	86.7 ± 5.4	80.0 ± 14.9
Degree of correction of the primary curve, %	62.0 ± 3.5	57.6 ± 10.1	63.8 ± 4.5
Number of patients with congenital scoliosis, n (%)	19 (41 %)	2 (20 %)	1 (16 %)
Number of patients with kyphotic deformities, n (%)	9 (19 %)	2 (20 %)	–
Preoperative neurological disorders, n (%)	7 (15 %)	3 (33 %)	3 (50 %)
Intraoperative hemorrhage, mL	502.1 ± 52.2	671.3 ± 164.1	730.0 ± 228.2
Number of decompressions, revisions, n (%)	1 (2.1 %)	1 (10 %)	1 (16 %)
Number of osteotomies, n (%)	6 (13 %)	1 (10 %)	–

is more pronounced in postoperative tests of pain sensitivity thresholds (thermoanalgesia). This suggested that for these patients, the prevailing possible risk factor in surgical correction of spinal deformities is preoperative dysfunction of the spinal tracts. Further study of the state of preoperative thermal and pain sensitivities will enable researchers to assess the possible risks of neurological complications.

Discussion

The results indicated that preoperatively, the state of thermal and pain sensitivities in patients with spinal deformities of different etiologies indicates a violation of the innervation status of the corresponding receptive fields on the skin. They are expressed to the greatest extent for dermatomes associated with the vertex of a spinal deformity, but are not localized within their limits, which correspond to earlier studies [26].

Surgical correction of spinal deformities has little effect on the average magnitude of the absolute values of thermal and pain sensitivity thresholds, but leads to a significant increase in the occurrence frequencies of thermoanesthesia and thermoanalgesia. In most patients in our sample, the deformity vertices and, therefore, the focus of surgical aggression were localized in the lower part of the thoracic spine, suggesting that thermoanesthesia and thermoanalgesia are mostly expressed in this region.

We found a correlation between the severity of violations in the perception of temperature and pain from heat and the reaction type of the spinal tracts to surgical aggression (Figure 4). This correlation corresponds to the conclusion made earlier on the relationship between the reaction type of the somatic motor system, the level of risk of development and reversibility of postoperative neurologic complications, and the severity of the final motor deficiency [25, 27].

Many studies have identified the following possible causes of neurological complications in surgery for spinal deformities: (i) congenital scoliosis, (ii) scoliosis with hyperkyphosis, (iii) deformity angle >90°, (iv) combined methods of surgery, (v) revision surgery, (vi) reduction of perfusion of the spinal cord due to hypotension or significant blood loss and vascular embarrassment, and (vii) preoperative neurologic impairment [8, 9, 14]. Procedures associated with a higher risk include osteotomy and kyphosis correction [7, 9, 28].

Analysis of the possibility of a connection between the seven causes of neurological complications in surgery for spinal deformities and the reaction types of the somatic motor system to surgery revealed that preoperative violation of the spinal tract function is the prevailing factor for increased risk of iatrogenic disorders, which is consistent with the results of other studies [29].

Conclusion

Changes in the state of thermal and pain sensitivity before and after surgical correction of spinal deformities are correlated with the proposed scale of the reaction types of the spinal tracts to surgical aggression. This relationship is more pronounced in postoperative tests of pain sensitivity thresholds. Consequently, preoperative determination of significant manifestation of thermoanalgesia can be considered a sign requiring increased attention from the surgeon and the neurophysiologist conducting IONM.

Information about the contribution of each author

E.N. Shchurova: collection and processing of material for esthesiometry, analysis of obtained data and literature, writing the text.

M.S. Saifutdinov: conception, study design, collection and processing of material for intraoperative monitoring of MEP, analysis of data obtained, writing the article text.

S.O. Riabykh: collection and processing of material for the treatment and evaluation of the clinical status of patients, analysis of the data obtained, writing the article text.

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