CELL THERAPY FOR SPINAL CORD CONTUSION INJURY: EVALUATION OF THE EFFICACY OF CRYOPRESERVED HUMAN UMBILICAL CORD BLOOD MONONUCLEAR CELLS IN A PRECLINICAL MODEL

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Objective. To evaluate the effect of systemic application of cryopreserved human umbilical cord blood mononuclear cells (hUCB-MNCs) in the acute period of spinal cord contusion injury (SCI) on the volume of zone of the spinal cord damage using high-field MRI.

Material and Methods. This study was performed on adult female Sprague-Dowley rats. Severe contusion SCI was modeled using the weight-drop method. Cryopreserved hUCB-MNC concentrate, stored in a cryobank for 3–4 years at –196 °C, was administered intravenously 1 day after injury. Locomotor behavior was assessed when animals moved in an open field using the BBB (Basso – Beatty – Bresnahan) scale for rats. MRI examination of the spinal cord was performed using a Clin Scan 7.0 T device.

Results. At week 6 after injury, a significant increase in the level of restoration of the motor function of the hind limbs (~10 %) was observed in the cell therapy group using hUCB-MNCs relative to the level of the self-healing group ($p < 0.05$). At the same time, the area of the posttraumatic cystic cavity decreased significantly (~45 %) and statistically significantly ($p < 0.05$), as well as its transverse (~38%) and longitudinal (~41 %) dimensions.

Conclusion. Cryopreserved hUCB-MNCs may be an effective and affordable means of cell therapy for contusion SCI when used in the acute period of injury.

Key Words: spinal cord injury; cell therapy; human umbilical cord blood mononuclear cells.

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Spinal cord injury (SCI), resulting in persistent deficits of motor, sensory, and vegetative functions in patients, is one of the most pressing problems in neurosurgery, traumatology, and neurorehabilitation.

In Russia, the mortality rate after such injury reaches 25–30 %, and the level of disability of the patients is 80–85 % [1, 2].

Current therapeutic approaches of SCI include decompression, therapeutic hypothermia, and pharmacotherapy [3–5]. Nevertheless, such treatment is not effective enough.

Cell therapy, including the use of allogeneic human umbilical cord blood mononuclear cells (hUCB-MNCs), is one of the promising treatment techniques for SCI [6–9].

The safety of clinical application of these cells has been repeatedly shown/proven [10, 11]. This allowed the International Association of Neurorestoratology (IANR) to recommend their use in clinical practice for the treatment of diseases or injuries of the central nervous system (CNS) [12].

Animal models provide an opportunity to study the effectiveness of cell therapy for treating SCI in vivo and are an essential step towards its clinical application. One such model of CNS injury that is clinically significant is spinal cord contusion, which accurately replicates this type of injury in humans and is relatively simple to perform in experiments [13–16].

This article presents data from MRI scans of the spinal cord and results on the recovery of hindlimb motor function in rats after severe spinal contusion treated with cryopreserved hUCB-MNCs in the acute period.

The objective is to evaluate the effect of systemic application of cryopreserved human umbilical cord blood mononuclear cells (hUCB-MNCs) in the acute period of spinal cord contusion injury on the volume of zone of the spinal cord damage using high-field MRI.

Material and Methods

This study was performed on adult female Sprague-Dawley rats weighing 230–250 g, received from the Pushchino

animal breeding complex (branch of the Shemyakin and Ovchinnikov Institute of Bioorganic Chemistry of the Russian Academy of Sciences). The animals were kept in individual cages under standard conditions of the experimental medical and biological clinic with a 12/12-hour light regime and unlimited access to water and food. All experimental records were approved in accordance with the ethical and scientific recommendations of the Ministry of Health of the Russian Federation (approval No. 267 dated March 19, 2006) and the National Standard of the Russian Federation GOST R 53434-2009 in accordance with the rules of maintenance and care of experimental animals, which is consistent with the European Directive 86/609/EEC, regulating the use of animals in research.

Modeling of spinal cord injury. Severe spinal cord contusion was simulated according to the "weight-drop" technique [16, 17]. Laminectomy at the T9 level was performed under general anesthesia (intraperitoneally with 5 % ketamine solution, 100 mg/kg, and 2 % xylosine solution, 20 mg/kg). The spine was fixed by the spinous processes of the T8 and T10 vertebrae. Severe spinal cord contusion was triggered by a free vertical fall from a height of 25 mm of a metal rod with a diameter of 2 mm and a weight of 10 g [18].

After SCI, the muscles and skin were sutured layer by layer (Fig. 1). In the early postoperative period (within 7 days), the animals underwent antibiotic therapy with gentamicin sulfate (1 mg/kg body weight, intramuscularly). In the case of a positive test for dehydration, 1 ml of 5 % glucose solution was administered, and if pain relief was necessary, ketoprofen 5 mg/kg was administered. Cytostatic agents were not used. In the first 3–5 days after surgery, manual massage of the abdominal wall was performed to empty the bladder until unassisted urination was restored.

Material for cell therapy. Cryopreserved hUCB-MNCs concentrate was stored for 3–4 years at -196 °C in a cryobank (Cryo-Center LLC, Moscow). Cell samples were thawed, cleared from cryoprotectant, and resuspended in saline solution according to the generally accepted technique [18]. Before injection, the number of live cells in the sample was 93–95 % (trypan blue stain).

Experimental groups. Injured animals were randomly divided into a self-healing group (n = 6; injection of 1 ml of saline solution into the tail vein one day after injury) and a cell therapy group (n = 5; injection of 10 million hUCB-MNCs in 1 ml of saline solution into the tail vein one day after injury).

Evaluation of the therapeutic effect of cell therapy. The recovery of voluntary hindlimb movements was evaluated in an open field of 75 × 125 cm for 4 min using the Basso, Beattie, Bresnahan (BBB) Locomotor Rating Scale (the BBB scale), which is a classification system of functional scores ranging from 0 to 21 (0 for absence of hindlimb movement, 21 for normal hindlimb movement) [20]. The evaluation was performed in a blind design by 2 independent examiners. The tests were performed weekly for five weeks starting on day 7 after injury.

Sensorimotor coordination of limb movements was evaluated in the Ledged Beam Test and on the Rotarod apparatus [21–23].

MRI. Conventional and quantitative MRI provide reliable visualization of the spinal cord and soft tissues, the location and extent of spinal cord injury caused by injury. Today, MRI is an indispensable tool in clinical diagnosis and prognosis in the evaluation of patients with SCI [24–26].

MRI were performed on a ClinScan 7.0 T (Bruker BioSpin, Germany), a specialized magnetic resonance imager for small laboratory animals. T2-weighted images were analyzed using the following scanning parameters: TR – 40 ms, TE – 29 ms, baseline resolution – 320 × 230, FOV – 45 32 mm, flip angle – 15°, slice thickness – 0.5 mm. MR images of post-traumatic cystic cavities at weeks 4 and 5 after injury in sagittal and frontal planes were analyzed using MicroDicom 3.9.5.666 (MicroDicom Ltd.), a software program widely used in clinical practice.

For quantitative analysis, we used mid-sagittal T2-weighted images (Fig. 2), where we measured the longitudinal and transverse dimensions of the post-traumatic cystic cavity (hyperintensity region) and calculated its area [27, 28].

Statistical analysis of the obtained data was performed using the Microsoft SPSS Statistics 25.0 software. The median and interquartile range for each of the measured parameters were used to describe the samples. The comparison of the two groups for all indicators was performed using the Mann-Whitney U test. Significance of differences was accepted at $p < 0.05$.

Results

Hindlimb paraplegia was recorded on day 1 after injury in both groups of injured animals. The recovery of hindlimb motor activity was significantly faster in animals receiving cell therapy than in the control group and was significantly different since week 2 after injury (Fig. 3).

At weeks 4, 5, and 6 after injury, the median and interquartile range of BBB points in the self-healing group were 5.0 (2.8; 6.5), 6.0 (3.8; 6.5), and 6.4 (3.8; 7.3), respectively, i.e., weak movements were observed in three joints: hip, knee, and ankle. The recovery of movements at the same period was 7.0 (6.0; 8.8), 7.0 (6.3; 9.0), and 7.0 (6.3; 9.3) points in the group of animals injected with hUCB-MNCs, which corresponds to intensive movements in the joints of the hindlimbs. Thus, administration of hUCB-MNCs significantly ($p < 0.05$) improves the recovery of hindlimb motor function compared to the self-healing group. It is worth pointing out that there was no positive effect of hUCB-MNCs in the Ledged Beam Test and Rotarod, since it is necessary to achieve in rats the ability to maintain body weight and coordination of movements of the fore- and hindlimbs in order to perform these tests.

The formation of intramedullary hematoma in the spinal cord tissue was recorded on day 2 after injury. Post-traumatic cystic cavities began to form in the animals at week 2 (Fig. 4), and typical post-traumatic cystic cavities (high intensity on T2-weighted images) formed from week 4 to week 6 after injury.

Measurements of the transverse size of the post-traumatic cystic cavity on T2-weighted MR images at week 4 after injury showed that the median and interquartile range were 1.43 (1.38; 1.46) mm in the self-healing group; 1.12 (0.97; 1.44) mm in the group of rats receiving cell therapy; 1.44 (1.29; 1.63) mm and 1.15 (1.01; 1.20) mm at week 5; and 1.33 (1.25; 1.46) mm and 0.97 (0.90; 1.36) mm at week 6, respectively (Fig. 5).

In other words, administration of hUCB-MNCs statistically significantly ($p < 0.05$) reduced the transverse size of the post-traumatic cystic cavity by 38% in animals with SCI.

An analysis of measurements of the longitudinal size of the post-traumatic cystic cavity on T2-weighted MR images at week 4 after injury showed that the median and interquartile range were 5.41 (4.09; 6.32) in the self-healing group, and 3.23 (3.04; 4.54) mm in the group of rats receiving cell therapy; 4.92 (3.82; 6.05) mm and 3.46 (3.28; 4.14) mm at week 5; and 5.12 (4.07; 6.25) mm and 3.62 (3.11; 4.97) mm at week 6, respectively (Fig. 6).

In other words, administration of hUCB-MNCs statistically significantly ($p < 0.05$) reduced the longitudinal size of the post-traumatic cystic cavity by 41% in animals with SCI.

The analysis of the cross-section area of the post-traumatic cystic cavity showed that its median and interquartile range at week 4 after injury was 6.2 (4.6; 6.8) mm^2 in the self-healing group and 3.3 (2.8; 3.9) mm^2 in the group of rats receiving cell therapy; 5.9 (4.4; 6.3) mm^2 and 3.0 (2.8; 3.7) mm^2 at week 5; and 5.9 (4.3; 6.3) mm^2 and 3.2 (2.8; 3.9) mm^2 at week 6, respectively (Fig. 7).

Therefore, administration of hUCB-MNCs statistically significantly ($p < 0.05$) reduced the cross-sectional area of the post-traumatic cystic cavity in rats with spinal cord contusion by up to 45 % compared to the control group.

Discussion

The search for new methods of SCI treatment is a difficult problem in neurosurgery [5, 29], as the possibilities of self-healing of damaged nerve tissue of spinal cord, as well as spinal cord functions in general, are very small.

This study demonstrates that administration of hUCB-MNCs in the acute SCI has a neuroprotective effect, enhancing both functional recovery of movement and reducing the dimension of post-traumatic cystic cavities. Our data show that just a single intravenous injection of hUCB-MNCs a day after injury provide restoration of hind limbs motion in rats to the level of extensive motion in three joints: ankle, knee, and hip. Some animals demonstrated plantar setting of a foot with body weight hold at rest, but still the animals were not able to hold their body weight when walking. This is consistent with the previously reported results used on the same SCI model [20, 30, 31]. Recovery of movements begins at week 2 after injury and stabilizes at weeks 5 and 6. The formation of the cystic cavity is completed by that time. This fact has been indicated in in other studies [10, 32, 33], but the size of the cavity is significantly smaller in the cell therapy group.

After SCI cell therapy, recovery of movements recovery starts earlier and progresses much faster, continuing the trend of improvement.

The formation of post-traumatic cystic cavity in rats begins from week 3 after injury, and by week 6 it is already formed, which is in line with the results obtained earlier in the histologic study by Basso et al. [16] and the MRI study by Metz et al. [15]; nevertheless, the post-traumatic cavity was significantly smaller in the rats in the cell therapy group than in the self-healing group.

The improved outcomes after SCI, as shown in our study, confirm that cell therapy with hUCB-MNCs has neuroprotective effects, but the mechanisms for

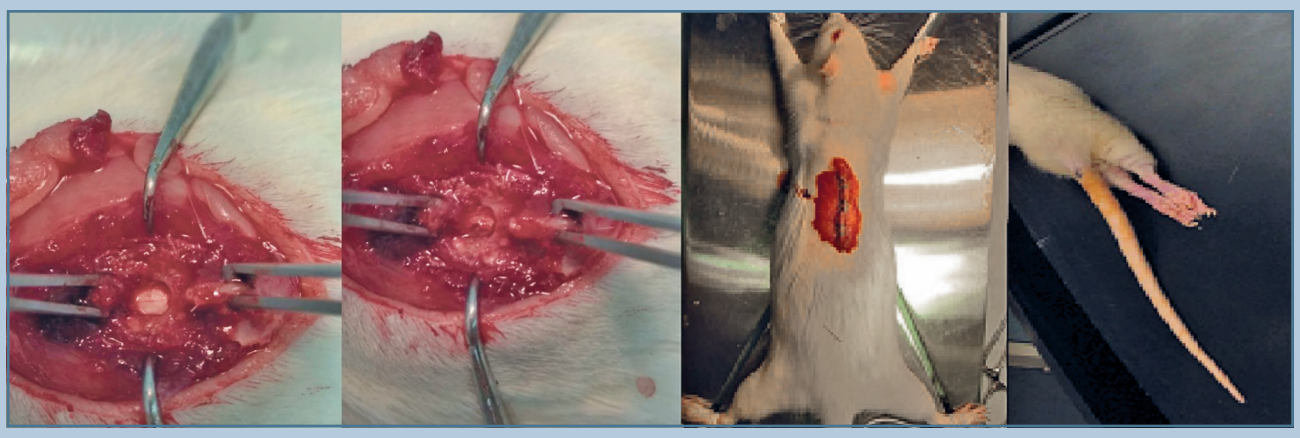

Fig. 1
Modeling of spinal cord contusion injury: spinal cord after laminectomy before injury, spinal cord after injury, animal after wound suturing, paraplegia of the hind limbs after injury

eliminating structural damage have yet to be investigated.

The hUCB-MNCs as a mean of cell therapy are attractive because of a number of advantages in their clinical application: availability for allogeneic transplantation in humans, weak immunogenicity, ease of obtaining, and the possibility of long-term storage (banking) and no ethical and legal restrictions for the use of these cells [11, 34–36].

The effectiveness of cell therapy using hUCB-MNCs demonstrated in this study is comparable and, in some cases, was superior to the effectiveness of cell therapy using other cells that are also recommended for clinical use, such as Schwann cells, olfactory membrane cells, neural progenitor cells, and bone marrow mononuclear cells [37–42].

Application of cryopreserved hUCB-MNCs does not require special equipment for clinical medical laboratories and special training of medical staff. The current cord blood banks (including those in Russia) allow easy delivery of hUCB-MNCs to neurosurgical departments of hospitals and their use in the acute SCI. From this aspect, hUCB-MNCs are a useful and realistic source for SCI cell therapy.

The limitations of the study were the small number of included animals and the lack of analysis of the mechanisms of neuroprotection found in cell therapy. These characteristics will be evaluated in the following studies. Nevertheless, significant differences in the volume of the spinal cord injury area between the experimental and control groups indicate the neuroprotective effect of cell therapy. Systemic cell therapy can significantly help reduce the size of the post-traumatic area of the spinal cord. This is probably due to the preservation of more spinal cord fibers in the area of the post-traumatic penumbra after the introduction of cells. If such specific therapy is not used, these fibers die and this leads to an increase in the size of the post-traumatic cyst. This is the manifestation of the neuroprotective effect of systemic cell therapy.

Conclusion

The obtained data indicate a real neuroprotective effect of human umbilical cord blood cells administered systemically in the acute period of severe spinal cord contusion in small animal models. The systemic application of cell therapy

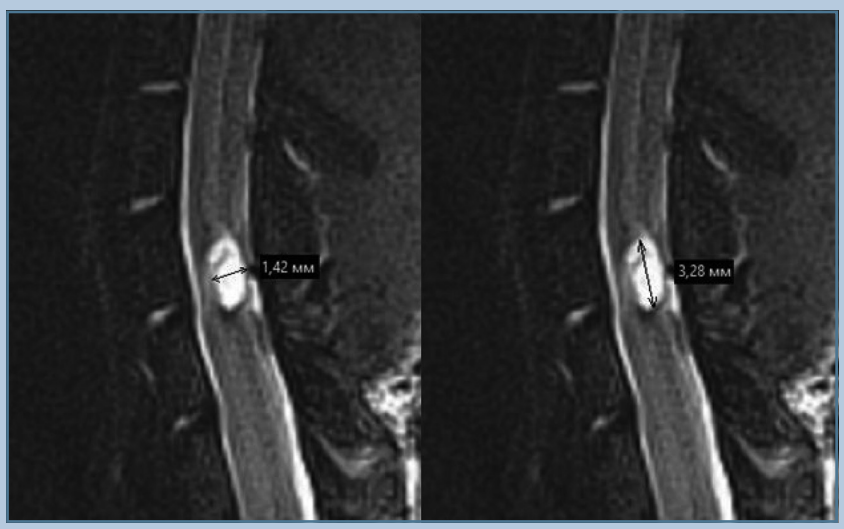

Fig. 2
Measurement of longitudinal and transverse dimensions of a posttraumatic cystic cavity on a sagittal section of a T2-weighted MRI image

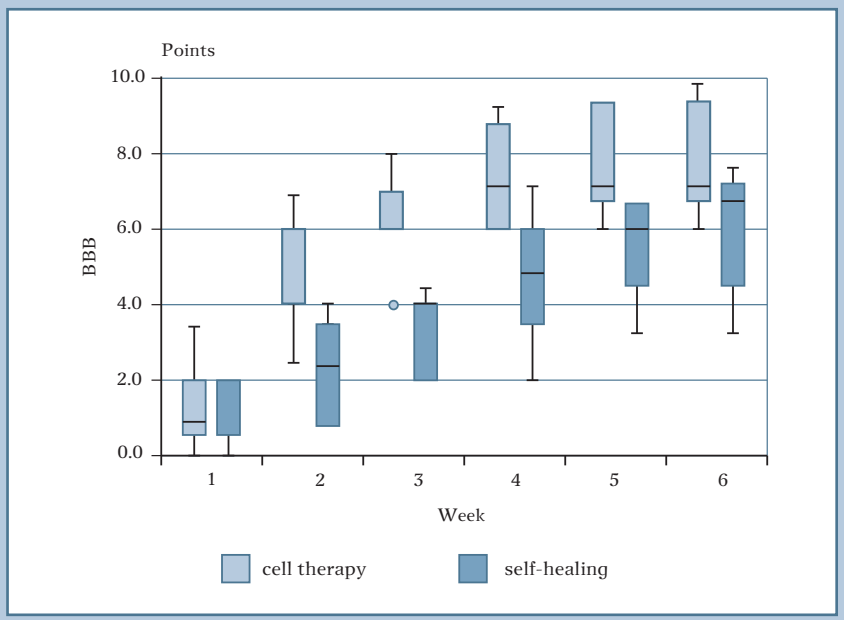

Fig. 3
Statistical analysis (box plot, median): dynamics of recovery of motor activity of the hind limbs in rats after spinal cord injury in the self-healing group and in the group of therapy with human umbilical cord blood mononuclear cells in the open field test according BBB scores

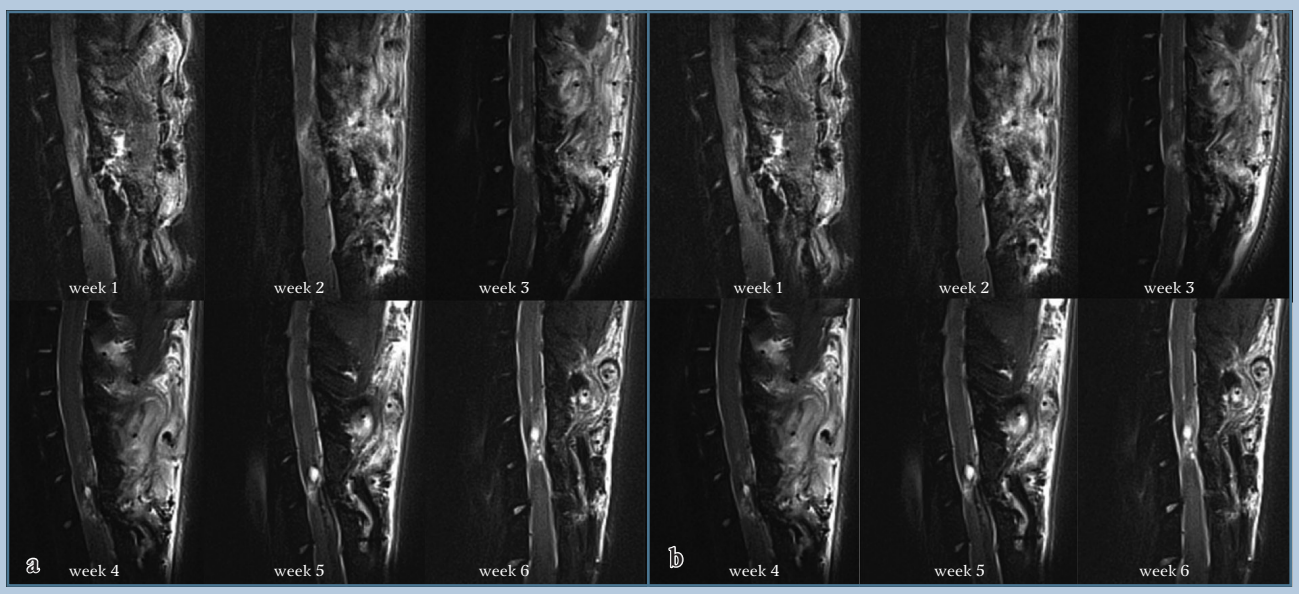

Fig. 4
An example of the development of a post-traumatic cystic cavity in rats from the self-healing group **(a)** and the cell therapy group **(b)**: sagittal T2-weighted MRI of a rat after spinal cord contusion injury, hyperintense signal with a clear border is a post-traumatic cystic cavity

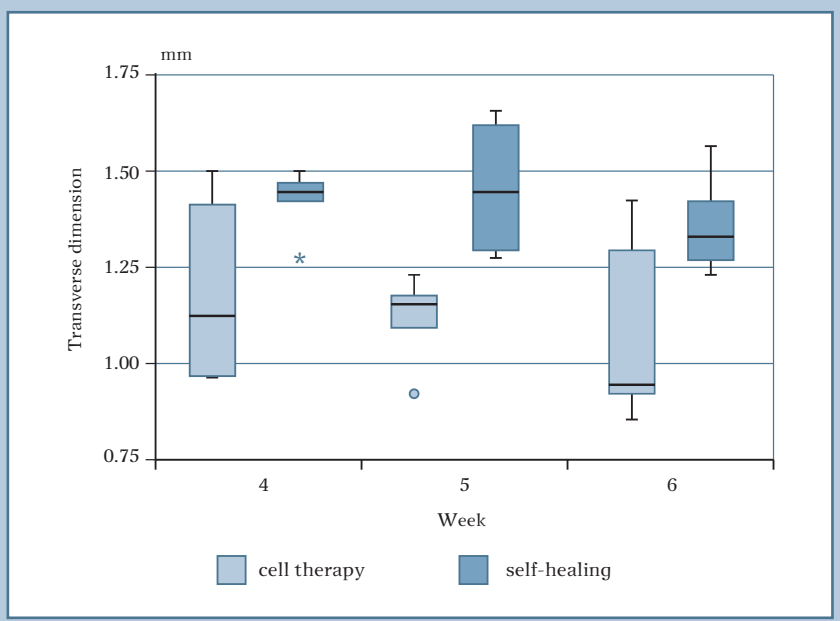

Fig. 5
Statistical analysis (box plot, median): transverse size of the cystic cavity at weeks 4–6 after injury in the self-healing group and in the group of therapy with human umbilical cord blood mononuclear cells; * $p < 0.05$

reliably promotes the reduction of post-traumatic spinal cord cyst volume. A single intravenous injection of hUCB-MNCs in the amount of 40–43 million cells per 1 kg of the patient's body weight preserves the structure of the nervous tissue of the spinal cord (neuroprotective effect) and provides a higher level of movement recovery after SCI (neurorestorative effect). It may be assumed that cryopreserved hUCB-MNCs can be used as a quite effective mean of cell therapy in the acute stage of spinal cord contusion.

The study was conducted under the research plan within the research program of the state task for 2024–2026: "Evaluation of the role of granulocytes and agranulocytes of human umbilical cord blood in the effectiveness of cell therapy with cryopreserved human umbilical cord blood cells for spinal cord contusion."
The authors declare that they have no conflict of interest.
The study was approved by the local ethics committees of the institutions.
All authors contributed significantly to the research and preparation of the article, read and approved the final version before publication.

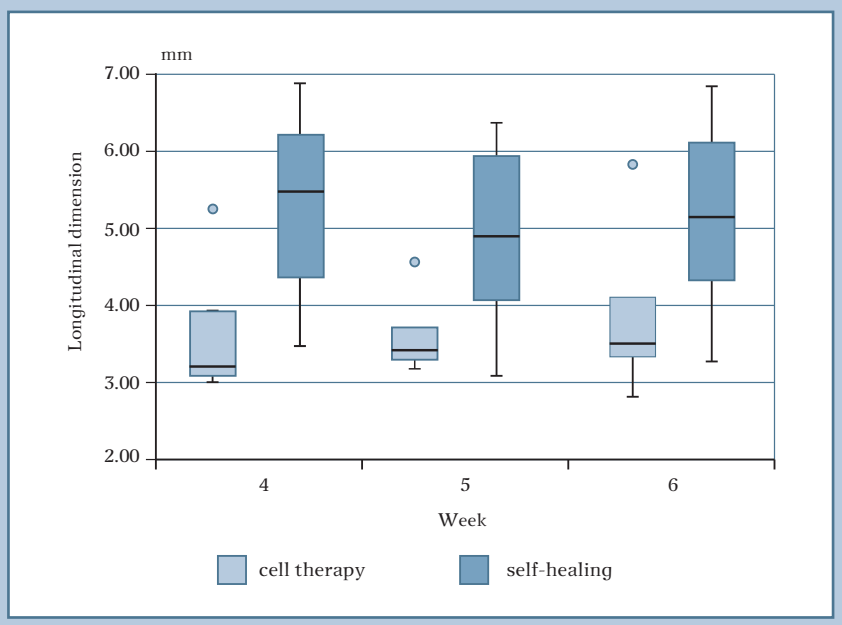

Fig. 6
Statistical analysis (box plot, median): longitudinal size of cystic cavity at weeks 4–6 after injury in the self-healing group and in the group of therapy with human umbilical cord blood mononuclear cells; * $p < 0.05$

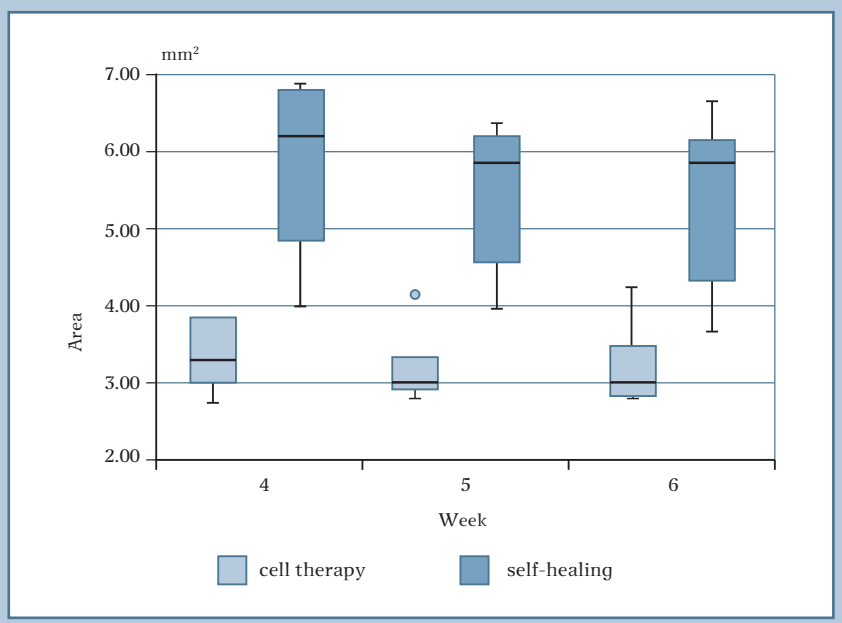

Fig. 7
Statistical analysis (box plot, median): cross-sectional area of the cystic cavity at weeks 4–6 after injury in the self-healing group and in the group of therapy with human umbilical cord blood mononuclear cells; * $p < 0.05$

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