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Cell therapy for patients with severe spinal cord injury (phase I/IIa): Assessment of safety and primary efficacy of therapy

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Background. The problem of pathogenetic treatment of spinal cord injury (SCI) is extremely acute, especially against the background of the growing number of SCI in modern conditions. The world literature widely presents the scientific research on the development and application of regenerative technologies and cell therapy effective for patients with SCI. One of the most promising areas is the use of stem cells. The human umbilical cord blood cells (HUCBCs) is one of the sources for obtaining stem cells having a number of serious advantages such as high efficiency in the patients' treatment with traumatic lesions of the central nervous system.

Aim. To evaluate the safety and primary efficacy of serial systemic (intravenous) administration of allogeneic mononuclear cells of the HUPBC to adult patients with gross neurological deficit because of acute period of severe contusion SCI.

Material and methods. Phase I of the SUBSCI I/IIa study included 10 patients (experimental and control groups) with severe SCI (cervical/thoracic/upper lumbar) in the acute period with gross neurological deficit (A/B on the ASIA scale). The conducted treatment included 4 systemic (intravenous) administrations of HUCBCs (allogeneic and compatible by AB0 and Rh factor) within 3 days from the moment of SCI, strictly after the primary surgical intervention. Observation period lasted 12 months after trauma. Safety assessment included the registration of all adverse events (AE) during the observation period with their further classification by severity (CTCAE v. 5.0) and potential connection with the cell therapy. The primary efficacy assessment was the identification of the neurological deficit dynamics (ASIA) – assessment of the restoration degree of motor and sensory functions of the lower extremities during the 1st year.

Results and discussion. A total of 419 AEs were detected in 10 patients, but only 2 of them (clinically insignificant) were assessed as probably related to cell therapy, the remaining 417 were not related to therapy. All patients had no signs of immunization to the administered HUCBCs samples. The analysis of the neurological deficit dynamics indicates the reliable restoration of motor functions in patients after cell therapy, compared with the control group.

Conclusion. Based on the results obtained, the systemic administration of allogeneic HUPBC, selected without taking into account the HLA system, can be considered as a safe and effective method for treating contusion SCI in the acute period.

Keywords: spinal cord injury (SCI), contusion spinal cord injury, traumatic injury of central nervous system, neurological deficit, regenerative therapy, cellular regenerative therapy (CRT), stem cell therapy, human cord blood mononuclear cells, human cord-placental blood, ASIA scale

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BACKGROUND

Spinal cord injury (SCI) is a severe lesion of the central nervous system, leading to the formation of a gross neurological deficit with significant decrease in the quality of life and persistent disability. In the active conditions of the modern world, there is a steady increase in the number of patients with SCI, especially in the most developed countries.

Annually in Russia an average of 70–90 adults suffered from SCI are registered per 1 million of the population. More than 200,000 patients have movement disorders due to a previous SCI, of which more than 35,000 have severe

movement disorders (para- or tetraplegia) [1, 2]. The incidence rates of SCI in other developed countries are uneven, but also remain high that is up to 27–83 cases per 1 million of the population in the USA and Canada [3], up to 18–30 in the countries of the European Union [4]. The greatest number of SCI cases is observed among the youngest and most able-bodied individuals. Thus, in Russia, more than 80 % of patients with SCI are under 30 years of age [1, 2]. In the USA, a bimodal age distribution is observed with the first peak occurs among patients aged 15–29 and the second – over 65.5 years [4, 5].

The available treatment methods for SCI are very limited in their effectiveness and are either symptomatic therapy or experimental. At the same time, the pathogenetic treatment methods approved by regulatory authorities in various countries and aimed at neuroprotection and/or neuroreparation of the spinal cord or affecting the key mechanisms of pathogenesis of the traumatic process are absent [2, 6]. The currently used treatment methods for SCI include surgical treatment, physical therapy, drug therapy, and regenerative technologies/cell therapy [6].

Given that SCI is a consequence of vertebral trauma, the surgery should be the mandatory first stage of treatment for every patient with SCI [7, 8]. However, in relation to the spinal cord, the surgical decompression and stabilization serve as palliative rather than pathogenetic treatment methods and are aimed at restoring the structure of the vertebral column, not the spinal cord [7, 9]. The surgical decompression and stabilization actually only provide conditions for self-healing of the spinal cord [8].

Many preclinical and clinical studies have shown that treatment outcomes in patients with SCI are better when surgery is performed earlier after the injury [6–8]. However, the degree of regression of neurological deficit and restoration of spinal cord function largely depends on the degree of the nervous system damage and remains low even if early and complete surgical decompression of the spinal cord and stabilization of damaged vertebral segments are performed [5].

The treatment methods such as physical (controlled hypothermia, hyperbaric oxygenation, exercise therapy) [8] and medication (glucocorticosteroids, nonsteroidal anti-inflammatory drugs, gangliosides, antioxidants, atorvastatin, calcium channel blockers, etc.) [10] are used, mainly aimed at secondary factors of damage. However, their effectiveness also remains low and does not provide a sufficient level of spinal cord functions restoration [10].

Moreover, many drugs may be contraindicated for patients or associated with serious side effects (with high frequency) [11]. The existing limitations in the treatment of SCI dictate an urgent need to develop the alternative effective and safe, ideally pathogenetic, treatment methods in the acute period.

In recent decades, the direction of developing the new regenerative technologies and cell therapy for SCI has been actively developing. The promising regenerative technologies include blockers of myelin-associated axon growth inhibitors (antibodies blocking Nogo A), soluble NgR, recombinant DNA vaccines, Rho inhibitors, as well as the use of various neurotrophic and neuroprotective factors (brain-derived neurotrophic factor, nerve growth factor, neurotrophins, etc.) [12].

In many preclinical and a number of clinical studies, all of the above-mentioned methods have shown their therapeutic effectiveness [12], although to a significant extent limited. Even a combination of several of the above-mentioned methods provides a relatively low degree of restoration of neurological functions in injured [13].

One of the most actively developing and promising areas is cellular regenerative therapy. The various types of stem cells have many therapeutic effects [14]:

- paracrine, realized through the secretion of trophic and protective factors;
- activation of endogenous stem cells and progenitor cells (ependymal neuronal stem cells in the case of SCI);
- direct neuroregenerative/neuroreparative;
- anti-inflammatory;
- angiogenic;
- potential differentiation of stem cells into cells of damaged structures.

Almost all types of stem cells implement the above-mentioned mechanisms, but the degree of implementation of each mechanism in the therapeutic effect differs in different types of cells [15]. Many preclinical and a number of clinical studies describe the therapeutic potential in the treatment of SCI of the following stem cells types – embryonic, induced pluripotent, neuronal and mesenchymal [15].

One of the most promising sources of stem cells for cell therapy is human umbilical placental blood cells (HUPBC) [16]. HUPBC have a number of advantages (compared to other sources of stem cells):

- by their nature, they are all postnatal, which completely eliminates any ethical restrictions [17];
- they are an easily accessible cryopreserved material suitable for long-term storage in frozen form in cryobank conditions;
- they are easily accessible in virtually unlimited quantities [18];
- sample preparation for administration is fast (up to several hours), does not require preliminary collection and cultivation of the patient's autologous cells;
- they are immunologically naive cells available for use in immunocompetent patients without taking into account the compatibility system HLA (Human Leukocyte Antigens – human leukocyte antigens responsible for the regulation of the immune response and tissue compatibility), which allows for unrelated treatment and the use of allogeneic cells;
- their administration can be carried out in various ways, including systemic (intravenous and intra-arterial) and local (intraspinal and intrathecal);

- they implement most of the listed therapeutic effects, with the exception of direct differentiation into nerve cells.

The most pronounced mechanisms of HUPBC action are the following: paracrine, realized through the secretion of protective, trophic and regenerative factors; immunomodulatory, aimed at preventing the infiltration of damaged areas of the spinal cord by neutrophils and macrophages [16].

The efficacy and safety of HUPBC use have been confirmed in many preclinical and clinical studies. The preclinical data from our group also confirm that in experiments on animal models of SCI, HUCBCs provide the restoration of the damaged spinal cord functions up to 63 % compared to the control group [18, 19].

The ongoing clinical trial "Systemic Umbilical Cord Blood Administration in Patients with Acute Severe Contusion Spinal Cord Injury" (SUBSCI, phase I/IIa) is divided into two parts: the first one is presented in this publication, the second will be described in subsequent ones.

The aim of the first part of this study was to evaluate the safety and primary efficacy of serial systemic (intravenous) administration of allogeneic mononuclear HUCBCs in adult patients with gross neurological deficit because of severe contusion SCI in the acute period.

MATERIAL AND METHODS

Study design and review

The study was prospective, single-center, open-label and conducted at the Scientific Department of Emergency Neurosurgery and Neurointensive Care Unit of the Sklifosovsky Research Institute of Emergency Medicine of the Moscow Health Department (hereinafter referred to as the Sklifosovsky Institute).

The samples of allogeneic mononuclear HUCBCs were obtained from Medical center "Dynasty" (Samara, Russia) within the framework of a scientific grant (No. 2312-18/22) of the "Moscow center innovative technologies in healthcare".

The study was approved by the Academic Council and the Ethics Committee of the Sklifosovsky Institute and Medical center "Dynasty", and also was registered on the www.ClinicalTrials.gov (identifier NCT04331405) [20].

The study included 10 patients with severe contusion SCI in the acute period and with the most expressed neurological deficit A/B according to the classification proposed by the American Spinal Injury Association (ASIA), with a range from A to E (A is the most severe neurological deficit, E is normal) [21]. The primary surgical treatment was performed in all patients within 3 days from the moment of injury. The study participants received 4 intravenous injections (at intervals of 1 week) of mononuclear HUCBCs (allogeneic, banked, unrelated, without taking into account the HLA antigen system), selected by blood group and Rh factor.

In each case, the first administration was performed no later than the first 3 days after the injury. During the recruitment period between patients № 3 and № 4, a 3-month break was made for data safety monitoring (Data Safety Monitoring Board, DSMB). After discharge, the observation period was 12 months, and patients were strongly recommended to undergo rehabilitation courses. During the entire observation period, all identified adverse events (AEs) were registered and analyzed by the research team and DSMB members.

Inclusion and exclusion criteria. This study included men and women aged 18 to 75 years with severe acute contusion SCI and gross neurological deficit, exclusively A or B according to the ASIA scale. The structure of the spine and SCI was assessed using computed tomography (CT) and magnetic resonance imaging (MRI).

This study included only patients with confirmed SCI (according to neuroimaging data). In addition, the mandatory condition for inclusion was the performance of the 1st stage of decompressive and stabilizing surgery for spinal injury within the first 3 days from the moment of injury.

The exclusion criteria were the following: severe concomitant injury (ISS >35); impairment of vital functions (artificial ventilation, severe hypotension/hypertensive support, uncontrolled arterial hypertension, acute myocardial infarction, etc.); failure of internal organs; immune system diseases (autoimmune diseases undergoing immunosuppressive therapy); identified allergic reactions to components of the HUCBCs samples; hematological diseases and persistent coagulopathy; burdened oncological history, presence of oncological diseases or unoperated benign tumors. A detailed list of inclusion and exclusion criteria is presented in Table 1.

SAFETY ASSESSMENT OF CELL THERAPY IN PHASE 1 OF THE STUDY

The DSMB was organized to assess the safety of cell therapy in phase 1 of the study. It included two neurosurgeons, a neurologist, an intensivist, and a clinical research specialist. The safety monitoring was performed every 2 months throughout the observation period of patients included in the study. More detailed monitoring was performed before the inclusion of patient № 4 in the study.

The unscheduled DSMB monitoring was performed after the death of patient № 5 (as a result of confirmed pulmonary embolism (PE) secondary to floating lower extremity vein thrombosis). All reported AEs were analyzed and discussed by the team members and graded using the CTCAE v. 5.0 protocol. The final review and analysis of AEs were performed at the end of the observational period, 12 months after SCI in the last patient (patient № 10).

Selection and preparation of human umbilical cord-placental blood cell samples. The HUCBCs samples were obtained from the accredited cord blood bank of State Budgetary Healthcare Institution Medical Center "Dynasty". The samples were selected taking into account the blood group and Rh factor. An additional (desirable, but

not mandatory) criterion was the possibility of selecting 4 samples from 1 donor for administration to 1 patient (to exclude potential cross-reactions when creating a chimeric mixture). The samples from 2 donors were selected for 3 patients.

Criteria for selection of HUCBCs samples:

1) TNCC >250 × 10^6, where TNCC is the total number of nucleated cells;
2) cell viability: more than 90 % (according to the results of the trypan blue test);
3) compatibility according to AB0 and Rh factor;
4) absence of any blood-borne infections;
5) general sterility.

All samples were collected with informed consent from donor mothers at least 6 months prior to sample collection. All collected samples successfully passed the quarantine period. The cells viability was assessed twice – during sample processing and after thawing. A viability of more than 92 % was considered acceptable.

The maternal blood tests were performed in the certified donor laboratory of Medical center "Dynasty", and included tests for antibodies to cytomegalovirus (CMV) IgM, hepatitis B (HBV), hepatitis C (HCV), herpes simplex virus (HSV) IgM, toxoplasma IgM, T-cell lymphotropic virus types I and II (IgG), human immunodeficiency virus (HIV) I and II and surface antigens of hepatitis B, syphilis, HIV I and II, CMV, HSV I and II, *Toxoplasma gondii* (335TOG) and HCV.

Only samples with negative results for all the above-mentioned agents were selected. Then the samples were frozen according to the standard protocol and stored in a Dewar container for at least 6 months before administration. The donors were subsequently re-examined for the above-mentioned infectious agents. After the end of quarantine, the samples were approved for clinical trials. The plasma of the HUCBCs was also tested for the presence of blood-borne infections and general sterility.

During the first stage, the collected samples were transferred from liquid nitrogen to nitrogen vapor for 12–24 h, then defrosted in Dextran 30–40 (JSC Biokhimik, Saransk, Russia), 5 % human serum albumin solution (JSC NPO Mikrogen, Moscow, Russia), and sterile saline (LLC Solopharm, St. Petersburg, Russia). The cooled HUCBCs solution was diluted to a volume of 45 ml. The tubes were centrifuged with cooling at 600 g for 10 min. The supernatant was removed and then resuspended in 10 ml of the solution.

To study the cell viability, 100 µl of cooled washed solution were collected. All samples with cell viability less than 92 % were disposed of. The resulting volume of cell concentrate was brought to 100 ml using a buffer solution, transferred to a sterile transfusion bag, and delivered to the Sklifosovsky Institute within 3 hours. The patients were administered HUCBCs in accordance with the standard transfusion protocol intravenously by drip.

SURGICAL TREATMENT

According to the inclusion/exclusion criteria, this study included only patients with severe contusion SCI in the acute period, admitted to the hospital no later than 3 days after receiving SCI. All studies, including CT and MRI, were performed within 3 hours after admission. The primary decompression of the spinal cord and stabilization of the damaged segments of the vertebral column were performed in all cases within 12–72 hours after trauma, taking into account the general condition of the patient and the severity of the injury. The first injection of HUCBCs was performed after the first stage of surgical treatment. The second stage of surgical intervention was performed in 5 cases within 1–3 months after trauma.

NEUROIMAGING

All patients underwent a comprehensive examination upon admission, including CT and MRI of the injured area of the spine and spinal cord. The study included patients with myelopathy diagnosis confirmed by MRI (the key criterion is the presence of a myelopathy focus at the level of injury). The attempt was made to perform MR tractography in 2 cases. However, the tractographic picture turned out to be uninformative both upon admission and after surgical treatment.

In the first case, this was due to spinal cord edema, whereas after surgery, the tractographic protocol was disrupted due to the proximity of metal structures to the area of interest, and the picture was distorted by artifacts. Subsequently, it was decided to exclude MR tractography from the list of examinations. The study participants underwent CT after surgery to determine the correctness of the fixation system installation and to control the adequacy of decompression. Then CT was repeated in 3, 6, and 12 months after SCI. The control MRI was performed in 6 and 12 months after SCI.

ADMINISTRATION OF HUMAN UMBILICAL CORD BLOOD CELL SAMPLES

The HUCBCs samples were delivered from the cryobank at 4 °C in a closed box, completely ready for administration. The shelf life of the HUCBCs samples was 3 hours from the moment of defrosting. The participants did not take immunosuppressants or myeloablative drugs during the entire study period. The participants were premedicated with a 1 % chloropyramine solution (0.5 mg/kg) 30 minutes before cell administration. The necessary medications, including antihypertensive, antiarrhythmic, antiallergic, steroid and antipyretic drugs, were available to patients if necessary.

The cell concentrate was administered through a peripheral venous catheter under constant medical supervision, strictly in accordance with standard requirements for transfusion of blood components, including individual and biological tests – 5 ml of HUCBCs concentrate was administered slowly (1 ml over 1–1.5 min) by drip followed

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Table 1. Inclusion and exclusion criteria for the SUBSCI I/IIa study*

Criteria	
inclusion	**exclusion**
1. Both males and females, 18 to 75 years old. 2. Contusion SCI at cervical, thoracic or upper lumbar (cone level) levels. 3. Acute period of SCI (first 3 days after trauma). 4. Presence of contusion SCI confirmed using MRI (T1- and T2-weighted images, STIR). 5. ASIA A/B neurological deficit. 6. Possibility of primary decompressive and stabilizing surgery with the following administration of 1st sample of HUCBCs during first 3 days after trauma. 7. The level of neurological deficit during first 3 days after SCI is the identical to this parameter at the moment of trauma. 8. Informed consent signed by the patient or his legal representative	1. Motor function preserved in lower limbs at admission (LEMS >0 points) or ASIA C, D or E deficit level. 2. The confirmed non-contusion character of SCI (according to MRI data). 3. Severe combined trauma (ISS >35 points). 4. Inability to perform the primary decompression of spinal cord and stabilizing of vertebral column as well as impossibility (for any reason) of 1st sample of HUCBCs infusion during first 3 days after SCI. 5. Persistent systolic arterial pressure (AP) >185 mmHg or diastolic AP >105 mmHg or need of aggressive AP lowering using systemic antihypertensive medication at the moment of patient inclusion. 6. Acute myocardial infarction. 7. Blood glucose level <3.5 Mmol/L or >21 Mmol/L. 8. Acute or deterioration of chronic diseases of central nervous system (CNS) (e. g. stroke, non-traumatic subarachnoid hemorrhages, intracranial hemorrhages and others CNS diseases at the discretion of investigator). 9. Hypotension – systolic AP <90 mmHg or need for intensive systemic inotropic therapy. 10. Objective need for artificial lung ventilation (ALV) at admission or prior to the surgery of 1st stage. 11. Acute kidney failure or deterioration of chronic kidney failure (creatinin level >250 mumol/L or carbamide level >25 Mmol/L). 12. Liver failure (general bilirubin level >25 mumol/L, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels >4 times exceeding upper reference limit). 13. Other significant disorders of vital functions. 14. Acute or deterioration of chronic diseases of internal organs preventing from HUCBCs samples infusion. 15. Autoimmune diseases (active or anamnestic). 16. History of allergic reactions of any type for any component of HUCBCs samples. 17. Pregnancy or lactation. 18. Significant surgeries or severe traumas within 3 months prior to patient inclusion in this study. 19. Acute or chronic infection diseases (tuberculosis, lues, HIV, hepatitis B, hepatitis C). 20. Moderate or severe hematological and/or oncohematological diseases. 21. Any known malignant tumors (both operated and not operated) or any clinical signs of malignant tumors revealed before inclusion in the study. 22. Any benign tumors (not operated or not totally removed) at the moment of patient inclusion in the study. 23. Neurological and/or psychiatric diseases preventing patient from complete understanding of study protocol or fulfillment of the study protocol requirements. 24. Other reasons preventing patient from complete understanding of study protocol or fulfillment of the study protocol requirements. 25. Patient's participation in any other clinical trials or studies within 6 months prior to inclusion in this study. 26. Constant immunosuppressive therapy for any reason. 27. History of any reaction for full blood or blood component transfusion. 28. Need for hemodialysis at the moment of admission. 29. History of bone marrow or internal organs (both donor and relative) transplantation. 30. Previous or current treatment using any regenerative technologies (grow factors, cytokines, cell therapy, gene therapy etc.). 31. Any other reasons preventing patient's inclusion according to the investigator's opinion

Note. *ASIA – American Spinal Injury Association scale with a range from A to E (A – the most severe neurological deficit, E – normal); ISS – index of severity of combined injury; LEMS – lower extremity motor score (maximum 50 points in 5 key muscle groups of the lower limbs); STIR – Short Tau Inversion Recovery (MRI mode); BP – blood pressure; ALT – alanine aminotransferase; AST – aspartate aminotransferase; HIV – human immunodeficiency virus; MRI – magnetic resonance imaging, HUCBCs – human umbilical cord blood cells; SCI – spinal cord injury; CNS – central nervous system.*

**https://ctv.veeva.com/study/cord-blood-cells-in-patients-with-acute-sci*

by a 5-minute pause to assess potential reactions. If no reactions occurred, the remaining volume was administered continuously by drip. The bags from the administered samples were stored at 4 °C for 72 h and then discarded if no reactions were recorded. The additional intravenous hydration therapy was also administered – 400–800 ml of physiological solution.

OBJECTIVES OF PART 1 OF THE STUDY

The primary objective is to assess the safety of systemic use of HUCBCs. For this purpose, all AEs were recorded during the first year after trauma in all patients included in the study. In addition, the potential cases of graft-versus-host disease (GVHD) symptoms were assessed during the entire observation period (12 months after trauma). The

Table 2. Baseline characteristics of patients included in the study as well as characteristics of administrated allogeneic human umbilical cord blood cells samples

Characteristics	Value
Patients	
Gender, *n* (%): male female	 9 (90.0) 1 (10.0)
Mean age (average range), years old	41.9 (25–66)
Mean weight (average range), kg	86.4 (58–122)
Severity of neurological deficit according to ASIA scale, *n* %	
ASIA A	6 (60.0)
ASIA B	4 (40.0)
ASIA C	0
ASIA D	0
ASIA E	0
Characteristics of cells HUCBCs, values range	
TNCC for 4 infusions, ($\times 10^9$)	1.2 (1.04–1.39)
TNCC for 1 infusion, ($\times 10^6$)	299.9 (252.6–378.1)
Administered cell dose, ($\times 10^7$) cell/kg	1.48 (0.89–2.14)
Cell viability level (trypan blue test), %	96.9 (93.2–99.1)
Administered viable CD34+ cells, ($\times 10^6$) cell/kg	1.21 (0.73–1.76)

Note. *TNCC – total number of nucleated cells. See note to Table 1.*

secondary objective is to assess the dynamics of the neurological deficit severity and the level of restoration of motor function of the lower extremities.

1. Safety assessment

The safety of the cell preparation usage was assessed daily during each infusion of HUCBCs throughout the entire period of inpatient treatment, and after discharge in 3, 6, and 12 months from the moment of trauma. During the inpatient stage of treatment, the condition of the patients was assessed daily by the researcher, and other specialists were involved if necessary. The next day after each administration, a set of blood and urine tests was performed (blood tests – general clinical, biochemical, and coagulogram, general urine analysis).

On the day of the cell preparation administration, the patients" condition was monitored immediately before administration, continuously during administration, every 15 minutes for the next 2 hours, every 30 minutes for the next 4 hours, and once for the next 6 hours in order to identify potential AEs and assess functional status.

All AEs registered during 12 months of observation were classified using the Common Criteria for Adverse Events (CTCAE v. 5.0) and summarized according to the severity and potential relationship of AEs with the cell therapy. In accordance with the CTCAE system, all AEs were divided into 5 categories by severity (grade 1–5): mild, moderate, severe, life-threatening, and fatal. Another parameter was the potential relationship between cell therapy and the identified AEs, which had four levels, including definitely unrelated (A), possibly related (B), probably related (C), and definitely related to cell therapy (D). The final analysis of AEs was performed by two investigators independently.

The additional safety assessment included determination of patients' immunization level to the injected HUCBCs samples (Coombs reaction). This assessment was performed in 5 patients during the final visit

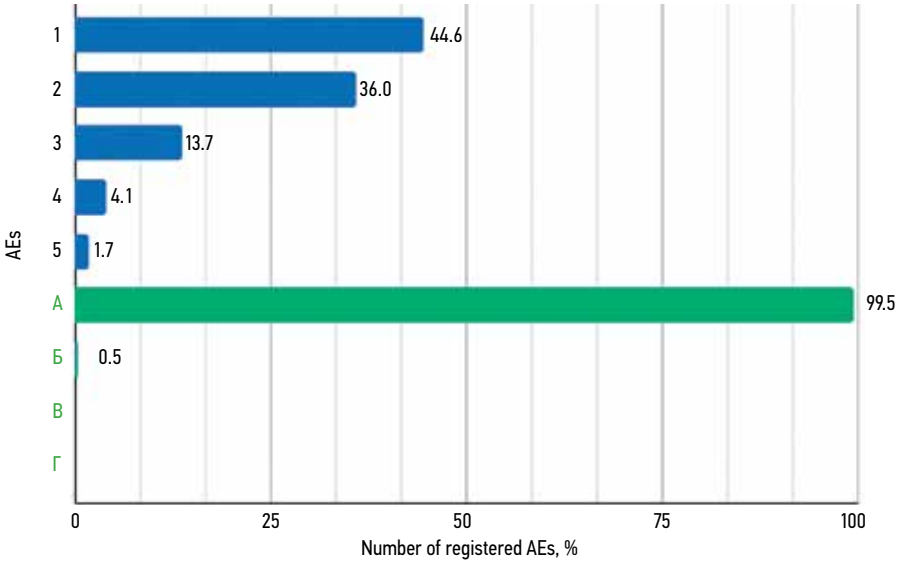

Fig. 1. *Summary of adverse events (AE) reported in 10 patients. The dependence of AE on their severity and the therapy with human umbilical cord blood cells is presented. AE severity levels: 1 – mild; 2 – moderate; 3 – severe; 4 – life-threatening; 5 – fatal. Levels of association between cell therapy and identified AE: A – definitely not related to cell therapy; B – possibly related; C – probably related; D – definitely related*

(12 months after injury). In addition, the possible clinical manifestations of GVHD were carefully monitored throughout the observation period (12 months).

2. Primary efficacy assessment

During the inpatient treatment, each patient underwent a daily general physical and neurological examination. After discharge, during follow-up visits, a joint examination was performed by two researchers. In Part 1 of the study, the main parameters assessed were the motor function of the lower extremities and the level of neurological deficit (ASIA), including 5 degrees of severity (ASIA A – the most severe deficit, ASIA E – no neurological deficit).

The muscle strength was assessed in 5 key muscle groups of the upper and lower extremities using a 5-point scale (0 points – plegia, 5 points – normal). The total result was assessed for the upper (upper extremities motor scale, UEMS), lower extremities (lower extremities motor scale, LEMS, with a maximum of 50 points in 5 key muscle groups of the lower extremities), as well as the total indicator. Due to the fact that the experimental group of patients was heterogeneous in terms of injury levels (cervical spine injury and neurological deficit in the upper extremities; thoracic and upper lumbar spine injury without deficit in the upper extremities, etc.), only the LEMS indicator was taken into account in the further analysis of primary efficacy.

The primary assessment of the neurological deficit level was performed in all patients during admission to the hospital. Only patients with a neurological deficit level of A or B according to the ASIA scale (the key indicator is the absence of motor functions below the level of injury) participated in the study. Subsequently, the motor function and the dynamics of neurological deficit were assessed daily during inpatient treatment and during follow-up visits after discharge from the hospital.

RESULTS

Characteristics of study participants

Part 1 of the SUBSCI I/IIa study included 10 adult patients, among them 9 men. The mean age was 41.9 years old (25–66 years old), mean weight was 86.4 kg (58–122). Three patients were included in the study from January 2015 to September 2015, the rest of them from January 2016 to February 2017. All patients were diagnosed with contusion SCI at the cervical (n = 4), thoracic (n = 4), or upper lumbar (n = 2) levels. The severity of neurological deficit corresponded to ASIA A (n = 6) or ASIA B (n = 4). The baseline LEMS level was 0 points in all cases. Self-care was not impaired in all patients before receiving SCI.

There were concomitant diseases that aggravated the severity of the traumatic process such as ankylosing spondylitis (n = 1) and degenerative stenosis of the vertebral canal at the cervical level (n = 1). The causes of injury were the following: fall from a height (n = 6), sport trauma (n = 2), diving (n = 1) and motorcycle accident (n = 1). The main characteristics of the patients included in this study are presented in Table 2, the initial individual characteristics are in Table 3.

SURGICAL TREATMENT

In half of the cases (n = 5), the 1st stage of surgical treatment was the only one (primary surgical decompression and stabilization of the damaged segments of the vertebral column), whole in others (n = 5) the 2nd stage of surgical treatment was required, which was performed in a delayed period (1–3 months after the injury).

The intraoperative blood loss and duration of operations were comparable in the subgroups of patients with SCI at both the cervical (75 ± 30 ml) and thoracic/upper lumbar (920 ± 240 ml) levels and did not affect the postoperative severity of neurological deficit. The patients had the similar baseline and postoperative neurological deficit according to the LEMS and ASIA scales. All patients were operated by neurosurgeons with comparable experience. All patients were in the intensive care unit for 1–9 days after surgery. The first administration of HUCBCs was performed on the day following the surgical intervention.

The first stage of surgical treatment. It was performed within 12–72 hours from the moment of injury. All patients underwent the following procedures:

- anterior decompression, reduction of dislocation (if any), corpectomy (if any), discectomy and anterior interbody cervical fusion with a plate and screws – in cases of SCI at the cervical level;
- laminectomy, spinal cord decompression, reduction of dislocation (if any), screw or combined hook-screw fixation of the damaged segment of the vertebral column – in cases of SCI at the thoracic and upper lumbar levels.

The second stage of surgical treatment. In all cases it was performed on average within 3 months after SCI (ranging from 3 weeks to 3 months). to restore the full support of the spine, it was required the following procedures in half of the patients (n = 5):

- additional posterior screw fixation in cases of contusion SCI of the cervical spine (n = 2);
- anterior thoracoscopic/thoracotomy or retroperitoneal discectomy/corpectomy and interbody fusion with a telescopic vertebral body prosthesis in cases of contusion SCI of the thoracic and upper lumbar spine (n = 3).

Table 4 presents the individual parameters of surgical treatment of patients included in the study and detailed information on the types and levels of vertebral and SCI, as well as a number of clarifying characteristics of the 1st and 2nd stages of surgical treatment.

THE HUMAN UMBILICAL CORD BLOOD CELLS ADMINISTRATION

All HUCBCs samples were compatible for blood group (AB0 system) and Rh factor (Rh). One of the exclusion criteria in this study was the presence of immune system

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Table 3. Individual characteristics of the included patients, human umbilical cord blood cells samples and surgical treatment methods

Patient (No.)	Age, years old	Gender	Weight at admission, kg	Type of Spine Injury (AO Spine classification)	Cause of injury	Neurological deficit severity at admission (ASIA scale)	TNCC infusion, ($\times 10^9$)	Administered cell dose, ($\times 10^7$) cell/kg	Number of infusions	Day of surgery*	Day of first HUCBCs administration*
1	43	M	122	Th6 fracture (A4)	Fall from a height 3.5 m	A	1.09	0.89	4	0	2
2	51	M	91	C7 dislocation (C), Th1 fracture (A3)	Fall from a height 1 m (concomitant ankylosing spondylitis)	B	1.20	1.32	4	1	2
3	65	M	112	Fractures of Th12, L1 (A4)	Fall from a height 3 m	A	1.18	1.06	4	2	3
4	29	M	74	Bilateral C4 dislocation (C), traumatic C4–C5 hernia	Sport injury (wrestling) + alcoholic intoxication	B	1.39	1.88	4	0	2
5	34	M	92	Th5 fracture – dislocation (C), Th6 fracture (A3)	Motorcycle accident	A	0.69	0.75	2	2	3
6	28	F	65	Bilateral Th11 (C), Th12 fracture (A1)	Sport injury (trampoline tumbling)	A	1.15	1.77	4	1	2
7	28	M	75	C5 fracture – dislocation (C), C6 fracture (A4)	Diving	A	1.23	1.64	4	1	3
8	25	M	58	Fractures of L1, L2 (A4)	Fall from a height 15 m	B	1.24	2.14	4	2	3
9	66	M	86	Fractures of Th2, Th3, Th4, Th6 (A2, A4)	Fall from a height 4 m	A	1.04	1.21	4	2	3
10	50	M	89	C5 dislocation (C), ruptured C5–C6 disc	Fall from a height 3 m (concomitant degenerative stenosis of the vertebral canal at the C4–C7 level)	B	1.28	1.44	4	1	3

Note. *F – female, M – male. See note to Tables 1, 2.*
**Day from the SCI.*

Table 4. Individual characteristics of patients included in the study as well as surgical treatment (stages 1 and 2)

Patient (No.)	Type of SI (AO Spine classification)	Stages of surgical treatment	
		1	2
1	Th6 fracture (A4)	Th5 laminectomy, combined hook-screw fixation of Th4–Th5–Th7–Th8	–
2	C7 dislocation (C), Th1 fracture (A3)	Discectomy C7–Th1, C7–Th1 fusion by plate	Posterior screw fixation C6–Th1
3	Fractures of Th12, L1 (A4)	Th12 laminectomy, L1, screw fixation of Th10–Th11–L2–L3	Thoracoscopic discectomy of Th11–Th12, Th12–L1, L1–L2, interbody fusion by cage
4	Bilateral C4 dislocation (C), traumatic C4–C5 hernia	Reduction of dislocation, C4–C5 discectomy, C4–C5 fusion by plate	–
5	Th5 fracture – dislocation (C), Th6 fracture (A3)	Combined hook-screw fixation of Th4–Th5–Th7–Th8–Th9	–
6	Bilateral Th11 (C), Th12 fracture (A1)	Reduction of dislocation, laminectomy Th11–Th12, screw fixation Th10–Th11–Th12–L1	Thoracoscopic discectomy of Th11–Th12, interbody fusion of Th11–Th12 by cage
7	C5 fracture – dislocation (C), C6 fracture (A4)	1. Corpectomy C6, C5–C7 fusion by plate. 2. Revision, discectomy C7–Th1, plate replacement C5–Th1	–
8	Fractures of L1, L2 (A4)	Laminectomy of L1 and L2, screw fixation Th11–Th12–L3–L4	Thoracoscopic corporectomy of L1, L2, interbody fusion of Th12–L3 by vertebral body prosthesis
9	Fractures of Th2, Th3, Th4, Th6 (A2, A4)	1. Laminectomy Th3, Th4, Combined hook-screw fixation of Th1–Th2–Th4–Th5–Th6. 2. Revision and wound drainage	–
10	C5 dislocation (C), ruptured C5–C6 disc	Corpectomy C5–C6, C4–C7 fusion by plate	Screw fixation of C4–C5–C6–C7 by lateral masses

Note. *SI – spinal injury. (–) stage 2 was not required. See notes to Tables 1, 2.*

disorders in the patient, so HLA compatibility did not need to be taken into account. All patients received 4 courses of HUCBCs infusions with TNCC = 1.48×10^7 ($(0.89–2.14) \times 10^7$), except for one patient (No. 5), who died on the 16th day after injury due to a confirmed episode of PE. This patient was excluded from further analysis of the effectiveness of cell therapy. However, given the 2 infusions of the cell preparation, the patient was included in the safety analysis.

THE COMMON CHARACTERISTICS OF THE ADMINISTERED HUCBCS SAMPLES ARE PRESENTED

In Table 2, and the individual characteristics of each sample injected into patients are presented in Table 3. All patients received a comparable total number of cells, relatively evenly divided into the four injections with an average of 1.2×10^9 (range $(1.04–1.39) \times 10^9$). Each injected sample contained a total of $(252.6–378.1) \times 10^6$ mononuclear cells (median 299.9×10^6). The average number of viable CD34+ cells injected was 1.21×10^6 (range $(0.73–1.76) \times 10^6$). The cell viability level both during storage and after thawing was more than 92 % in all samples used, with an average of 96.9 (93.2–99.1) %.

SAFETY ASSESSMENT OF SYSTEMIC CELL THERAPY

Based on the analysis results, 419 AEs were identified in 10 patients during the observation period (12 months); the average value for each patient was 34.6 (14–72) AEs.

All AEs registered during 12 months of observation were classified according to the CTCAE (v. 5.0) criteria, in accordance with the severity of the AEs, as well as the potential connection of the AEs with the cell therapy (Figs. 1 and 2, Table 5).

We note the inverse relationship between the number and severity of AEs, i. e. fewer severe AEs were registered: mild – 187; moderate – 151; severe – 57; life-threatening – 17; critical (fatal) – 7.

In the vast majority of cases, AEs were either a consequence of SCI or concomitant pathologies identified in patients after discharge. The incidence of registered AEs in 10 patients was the following: gastrointestinal disorders – 87 (20.8 %); nervous system disorders – 50 (11.9 %);

laboratory abnormalities – 49 (11.7 %); infections and infestations – 45 (10.7 %); general disorders – 31 (7.4 %); blood system disorders – 30 (7.2 %); metabolic and nutritional disorders – 28 (6.7 %); vascular disorders – 17 (4.1 %); renal and urinary tract disorders – 15 (3.6 %). The incidence of other AEs was less than 3 %. The diagram reflecting the distribution of registered AEs by groups is presented in Fig. 2.

Grade 4 adverse events (life-threatening). There were identified 17 such AEs, including 4 cases of anemia (severe, Hb <60 g/L), which developed in 3 patients after surgery and in 1 after PE. The remaining grade 4 AEs included cases of implant-associated inflammation (n = 2) and soft tissue infection at the surgical site (n = 1), related to postoperative cerebrospinal fluid leakage. In both cases, revision surgeries and therapy with broad-spectrum antibiotics (and their combinations) were performed. The grade 4 neurological complications consisted of 10 cases of lower paraplegia, which were apparently related to SCI.

Grade 5 adverse events (fatal). All such AEs were recorded in 1 patient, who died on the 16th day after the

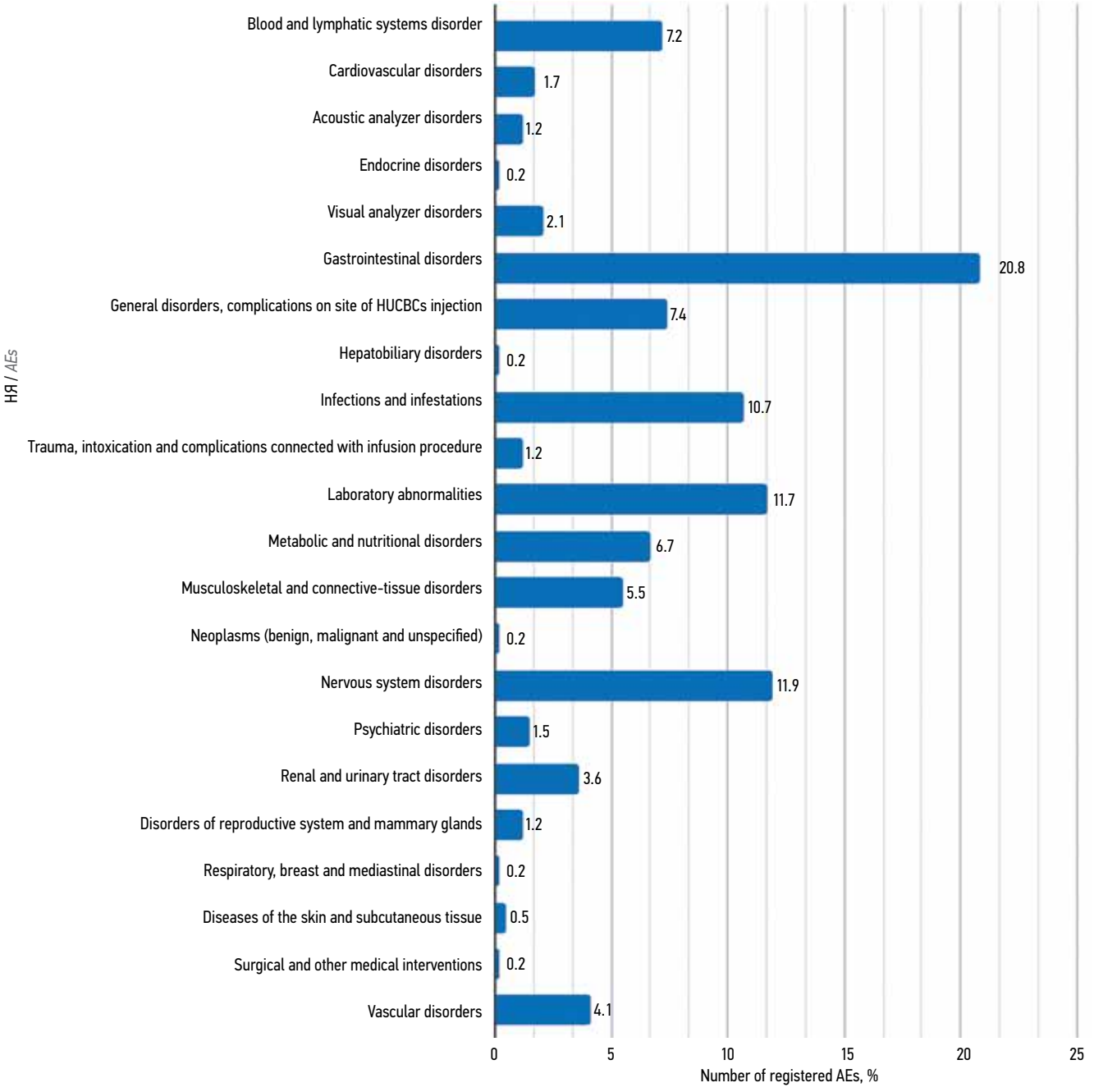

Fig. 2. *Frequency of adverse events (AEs) reported in 10 patients included in the SUBSCI study during 12 months of follow-up (CTCAE classification, v. 5.0). HUCBCs – human umbilical cord blood cells*

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Table 5. List of all adverse events (419) reported in patients (n = 10), classified according to CTCAE (v. 5.0) criteria and divided by severity into 5 degrees

CTCAE (v. 5.0)	Grade					Common number of AEs	Number of patients with AEs
	1	2	3	4	5		
Blood and lymphatic systems disorders							
Anemia	7	5	3	4	–	19	7
Disseminated intravascular blood coagulation	–	1	–	–	–	1	1
Others: leucocytosis less than 100.000/mm^3	8	2	–	–	–	10	10
Total	**15**	**8**	**3**	**4**	**–**	**30**	*
Cardiovascular disorders							
Asystole	–	–	–	–	1	1	1
Auriculoventricular block 1 grade	1	–	–	–	–	1	1
Disorders of heart conduction	–	1	–	–	–	1	1
Right ventricular dysfunction	–	–	–	–	1	1	1
Sinoventricular tachycardia	2	1	–	–	–	3	3
Total	**3**	**2**	**–**	**–**	**2**	**7**	*
Acoustic analyzer disorders							
Hearing loss	1	1	–	–	–	2	2
Otitis media	–	2	–	–	–	2	1
Vestibular disturbance	–	1	–	–	–	1	1
Total	1	4	–	–	–	5	*
Endocrine disorders							
Cushing syndrome	1	–	–	–	–	1	1
Total	**1**	**–**	**–**	**–**	**–**	**1**	*
Visual analyzer disorders							
Cataract	–	–	1	–	–	1	1
Eye pain	1	–	–	–	–	1	1
Keratitis	2	–	–	–	–	2	1
Retinopathy	–	1	–	–	–	1	1
Visual impairment	–	3	1	–	–	4	4
Total	**3**	**4**	**2**	**–**	**–**	**9**	*
Gastrointestinal disorders							
Abdominal pain	2	–	1	–	–	3	3
Anal bleeding	–	1	–	–	–	1	1
Abdominal distention	4	2	–	–	–	6	4
Colitis	–	1	–	–	–	1	1
Constipation	6	3	2	–	–	11	6
Diarrhea	7	4	1	–	–	12	8
Dry mouth	1	1	–	–	–	2	2
Duodenal ulcer	–	1	–	–	–	1	1
Dyspepsia	4	–	–	–	–	4	2
Faecal incontinence	2	6	–	–	–	8	8

Continuation of table 5

CTCAE (v. 5.0)	Grade					Common number of AEs	Number of patients with AEs
	1	2	3	4	5		
Gaseous distention	3	4	–	–	–	7	7
Stomach ulcer	–	1	–	–	–	1	1
Gastritis	8	2	–	–	–	10	8
Gastroesophageal reflux disease	3	1	–	–	–	4	2
Gastroparesis	2	–	–	–	–	2	2
Hemorrhoidal bleeding	2	–	–	–	–	2	2
Haemorrhoids	–	1	–	–	–	1	1
Nausea	1	–	–	–	–	1	1
Pancreatitis	–	1	–	–	–	1	1
Paradontosis	2	–	–	–	–	2	2
Tooth ache	3	1	–	–	–	4	3
Vomiting	2	1	–	–	–	3	3
Total	**52**	**31**	**4**	**–**	**–**	**87**	*
General disorders, complications on site of injection							
Chills	1	1	–	–	–	2	2
Fatigue	3	–	–	–	–	3	3
Fever	8	1	–	–	–	9	6
ARI symptoms	2	3	1	–	–	6	6
Pain	4	4	1	–	–	9	9
Other: transient hyperthermia less than 38 °C after administration of cell concentrate	2	–	–	–	–	2	2
Total	**20**	**9**	**2**	**–**	**–**	**31**	*
Hepatobiliary disorders							
Cholecystitis	–	1	–	–	–	1	1
Total	**–**	**1**	**–**	**–**	**–**	**1**	*
Infections and infestations							
Appendicitis	–	–	1	–	–	1	1
Bladder infections	–	5	2	–	–	7	5
Bronchial infections	–	2	1	–	–	3	3
Catheter-associated infections	–	1	–	–	–	1	1
Conjunctivitis	1	–	–	–	–	1	1
Implant-associated infections	–	–	–	1	–	1	1
Kidney infections	–	2	1	–	–	3	1
Laryngitis	–	1	–	–	–	1	1
Lung infections	–	–	2	–	–	2	2
Otitis media	–	2	–	–	–	2	1
Penile infections	1	–	–	–	–	1	1
Pharyngitis	–	1	–	–	–	1	1

Continuation of table 5

CTCAE (v. 5.0)	Grade					Common number of AEs	Number of patients with AEs
	1	2	3	4	5		
Salivary gland infections	–	1	–	–	–	1	1
Sinusitis	–	–	1	–	–	1	1
Soft tissue infections	–	–	–	1	–	1	1
Urethral infections	–	3	2	–	–	5	4
Urinary tract infections	–	8	4	–	–	12	5
Other: implant-associated suppurative inflammation	–	–	–	1	–	1	1
Total	**2**	**26**	**14**	**3**	**–**	**45**	*
Trauma, intoxication and complications of manipulations							
Intraoperative bleeding	–	–	1	–	–	1	1
Seroma	1	–	–	–	–	1	1
Wound complications	1	1	–	–	–	2	2
Diastasis of wound edges	–	1	–	–	–	1	1
Total	**2**	**2**	**1**	**–**	**–**	**5**	*
Laboratory abnormalities							
Increased APTT	6	4	–	–	–	10	10
Increased ALT	4	1	–	–	–	5	4
Increased alkaline phosphatase	1	–	–	–	–	1	1
Increased AST	3	1	–	–	–	4	4
Increased total bilirubin	1	–	–	–	–	1	1
Increased troponin (T)	–	–	1	–	–	1	1
Increased CPK	–	–	1	–	–	1	1
Increased creatinine	2	1	–	–	–	3	3
Decreased fibrinogen	2	–	–	–	–	2	2
Increased INR	4	–	1	–	–	5	5
Decreased platelet count	1	1	1	–	–	3	3
Increased serum amylase	1	–	–	–	–	1	1
Weight loss	2	2	6	–	–	10	10
Other: increased D-dimer	–	1	1	–	–	2	2
Total	**27**	**11**	**11**	**–**	**–**	**49**	*
Metabolic and nutritional disorders							
Acidosis	2	–	1	–	1	4	4
Dehydration	1	2	–	–	–	3	3
Hyperglycemia	4	–	1	–	–	5	5
Hyperkalemia	1	–	–	–	–	1	1
Hyperlipidemia	2	–	–	–	–	2	2
Hypernatremia	2	–	–	–	1	3	3
Hypoalbuminemia	5	2	1	–	–	8	8

Continuation of table 5

CTCAE (v. 5.0)	Grade					Common number of AEs	Number of patients with AEs
	1	2	3	4	5		
Hypocalcemia	2	–	–	–	–	2	2
Total	*19*	*4*	*3*	–	*2*	*28*	*
Musculoskeletal and connective-tissue disorder							
Muscle spasms	4	1	1	–	–	6	6
Myalgia	1	2	2	–	–	5	5
Osteoporosis	3	1	–	–	–	4	4
Pain in extremities	3	2	2	–	–	7	7
Scoliosis	1	–	–	–	–	1	1
Total	**12**	**6**	**5**	**–**	**–**	**23**	*
Neoplasms (benign, malignant and unspecified)							
Other: surgically removed intestinal polyps	–	1	–	–	–	1	1
Total	**–**	**1**	**–**	**–**	**–**	**1**	*
Nervous system disorders							
Brachial plexopathy	–	1	–	–	–	1	1
CSF leakage	1	–	–	–	–	1	1
Head ache	3	1	–	–	–	4	4
Neuralgia	–	1	1	–	–	2	2
Paresthesia	1	2	–	–	–	3	3
Seizures	–	–	–	–	1	1	1
Spasticity	4	3	1	–	–	8	8
Compression of spinal cord	–	–	–	10	–	10	10
Decrease of tendon reflexes	2	8	–	–	–	10	10
Other: lower paraplegia as a consequence of SCI	–	10	–	–	–	10	10
Total	**11**	**26**	**2**	**10**	**1**	**50**	*
Psychiatric disorders							
Anxiety	1	–	–	–	–	1	1
Depression	3	–	1	–	–	4	4
Euphory	–	1	–	–	–	1	1
Total	**4**	**1**	**1**	**–**	**–**	**6**	*
Renal and urinary tract disorders							
Glycosuria	2	–	–	–	–	2	2
Hematuria	1	1	–	–	–	2	2
Proteinuria	4	1	–	–	–	5	5
Kidney stones	–	1	–	–	–	1	1
Incontinence of urine	2	3	–	–	–	5	5
Total	**9**	**6**	**–**	**–**	**–**	**15**	*
Disorders of reproductive system and mammary glands							
Erectile dysfunction	–	–	4	–	–	4	4

End of table 5

CTCAE (v. 5.0)	Grade					Common number of AEs	Number of patients with AEs
	1	2	3	4	5		
Menstrual disorders	–	1	–	–	–	1	1
Total	**–**	**1**	**4**	**–**	**–**	**5**	*
Respiratory, breast and mediastinal disorders							
Other: postoperative hydrothorax	–	–	1	–	–	1	1
Total	**–**	**–**	**1**	**–**	**–**	**1**	*
Diseases of the skin and subcutaneous tissue							
Other: superficial bed-sores in gluteal and calcaneal areas	–	1	1	–	–	2	2
Total	–	*1*	*1*	–	–	*2*	*
Surgical and other medical interventions							
Other: migration and/or implant rejection	–	–	1	–	–	1	1
Total	**–**	**–**	**1**	**–**	**–**	**1**	*
Vascular disorders							
Hematoma	–	1	1	–	–	2	2
Hypertension	1	3	–	–	–	4	4
Hypotension	2	2	–	–	1	5	5
tromboembolic complications	–	–	–	–	1	1	1
Other: deep vein thrombosis	3	1	1	–	–	5	5
Total	**6**	**7**	**2**	**–**	**2**	**17**	*
TOTAL	***187***	***151***	***57***	***17***	***7***	***419***	*

Note. *APTT – activated partial thromboplastin time; CPK – creatine phosphokinase; INR – international normalized ratio; AE – adverse events; ARVI – acute respiratory viral infection; CSF – cerebrospinal fluid. AE severity grades: 1 – mild, 2 – moderate, 3 – severe, 4 – life-threatening, 5 – fatal AE. (–) no; (*) data in the corresponding column cannot be summed up, since some AEs could be registered in one patient several times during 12 months of observation, which means that the number of patients with AEs could be less than the total number of AEs. See note to Table 1.*

injury due to massive PE against the background of floating thrombosis of the lower extremities' veins. The cause of death was confirmed by forensic examination data. This patient was not included in further analysis of the effectiveness of cell therapy. A detailed list of the identified AEs is presented in Table 5.

Potential association of adverse events with the cell therapy. According to the analysis of all 419 AEs in 10 patients during the observation period (12 months), no definitely related or probably related AEs were identified. Two AEs were classified as "possibly related" – in both cases, it was short-term subfebrile hyperthermia (<38 °C) within 3 hours after the administration of HUCBCs. No additional medications or other interventions were required to stop the hyperthermia. The remaining 417 AEs were classified as "definitely not related to the cell therapy". Detailed information on the structure of the relationship between the identified AEs and the cell therapy is presented in Fig. 1 and Table 5.

During the analysis of potential GVHD manifestations during the entire observation period, no cases were identified. General symptoms of GVHD, skin reactions, manifestations from the liver and digestive organs were taken into account. At the end of the observation period, an indirect Coombs reaction was performed in 5 patients with the injected cell samples to exclude the effect of immunization. In all 5 cases, the result was negative, which confirms the immunological naivety of the mononuclear HUCBCs and the absence of immunization to the administered samples in all examined patients.

PRIMARY ASSESSMENT OF CELL THERAPY EFFICACY

Two interrelated parameters were assessed – the severity of neurological deficit (ASIA) and lower limb motor function (LEMS). At baseline, all patients included in the study had an ASIA deficit level of A or B and 0 points according to the LEMS scale.

Table 6. Initial evaluation of the cell therapy efeectiveness

Patient (No.)	Severity of neurological deficit (ASIA)			Difference in the severity of neurological deficit between baseline and in 12 months (ASIA), scores	Motor functions (LEMS), scores	
	baseline	in 6 months	in 12 months		baseline	in 12 months
1	A	C	C	2	0	14
2	B	D	E	3	0	50
3	A	D	D	3	0	39
4	B	D	E	3	0	50
5	A	–	–	–	0	–
6	A	B	B	1	0	0
7	A	C	C	2	0	9
8	B	D	D	2	0	46
9	A	C	C	2	0	26
10	B	D	D	2	0	45
Mean value				**2,2**	**0**	**31**
Range				**1–3**	**0–0**	**0–50**

Note. *See notes to Table 1*

Severity of neurological deficit. The analysis was performed in 9 patients, since 1 patient was excluded from the efficacy analysis after an episode of PE. All patients demonstrated a good response to cell therapy, except for one patient. Most patients (n = 5 (56 %)) showed an increase in ASIA by 2 points: from ASIA A to C (n = 3 (30 %)) or from ASIA B to D (n = 2 (22 %)). Some patients (n = 3 (30 %) showed an increase in ASIA by 3 points: from ASIA B to E (n = 2 (22 %)) or from ASIA A to D (n = 1 (11 %)). A patient with a complete linked dislocation of the Th11 vertebra showed ASIA level B (baseline – ASIA A) – she had partial recovery of deep sensitivity.

However, there was no recovery of motor function. After the end of the observation period (12 months), this patient showed further regression of neurological deficit to the ASIA C (2 years 4 months after SCI). The movements in the lower limbs with muscle strength up to 1–2 points appeared, which, however, did not affect the ability to verticalize and move independently. However, we did not take this result into account in our analysis, since these symptoms appeared after the observation period. The average level of regression of neurological deficit on the ASIA scale was 2.2 points (the range was 1–3 points).

Dynamics of motor function restoration in the limbs. In 6 patients (67 %), the LEMS score exceeded 25 points after 12 months. The threshold of 25 points is critical for patients with SCI – this is the minimum value for independent verticalization. In 2 patients (22 %), the complete restoration of spinal cord functions was noted – the LEMS score reached 50 points (normal), and the severity of neurological deficit regressed to ASIA E (no deficit). In 2 other patients, partial restoration of motor function was revealed – 14 and 9 points according to the LEMS scale.

In 1 patient, there was no effect of cell therapy on motor function – by the end of the observation period (12 months after injury), the LEMS score was 0 points; after 2 years 4 months – 6 points. The summarized average LEMS level at the end of the observation period was 31 points (range 0–50 points). A detailed description of the neurological status and treatment outcomes is presented in Table 6.

Neurological outcomes of treatment of patients with severe acute contusion SCI after therapy with HUCBCs were analyzed by comparing baseline parameters, as well as data in 6 and 12 months after injury.

The LEMS score was assessed on a 5-point scale in 5 key lower limb muscle groups. All patients had a baseline score of 0, corresponding to ASIA level A or B. The baseline values were assessed at admission and before primary surgery. The values were assessed by telephone or personal visits in 6 months and by personal visits in 1 year after completion of the follow-up period.

DISCUSSION AND LITERATURE REVIEW

The presented open-label, randomized, phase 1 clinical trial (SUBSCI I) aimed to evaluate the safety and primary efficacy of cell therapy administered to 10 adult patients with severe acute contusion SCI (cervical/thoracic/upper lumbar) and severe neurological deficit (ASIA A or B). Four intravenous injections of allogeneic cryopreserved banked mononuclear HUCBCs, matched by blood type and Rh factor, but excluding HLA (antigen compatibility), were administered. The average dose of viable mononuclear

HUCBCs was 1.48×10^7 cells. The first injection in the course was performed no later than 3 days after the injury.

The exact effective therapeutic dose of mononuclear HUCBCs for systemic cell therapy of acute contusion SCI remains unknown. In the case of the presented study, the doses were determined empirically, taking into account the available safety and efficacy information in other registered clinical trials [22]. It is important to note that the total number of nucleated cells received by the participants and divided into 4 infusions was comparable to the single dose administered to patients in other clinical trials, for example, in the clinical trial of D.T. Laskowitz et al. [22], the single infusion included $(0.83–3.34) \times 10^7$ cells.

The main objective of the first phase of the study was to evaluate the safety of cell therapy. The analysis of all AEs identified during the observation period (12 months) demonstrated that systemic administration of allogeneic cryopreserved banked mononuclear HUCBCs, matched by group and Rh factor, but without taking into account HLA antigen compatibility, was safe and well tolerated by all patients included in the study. The vast majority of registered AEs were mild (187 (44.6 %)) and moderate (151 (36.0 %)).

There were significantly fewer severe AEs (57 (13.7 %)) and life-threatening AEs (17 (4.1 %)). One patient had 7 (1.7 %) grade 5 AEs (due to fatal massive PE) against the background of floating thromboses of the lower extremities' veins (see Table 5). The postmortem examination data confirmed that the cause of death was PE, which led to the development of all identified grade 5 AEs.

Grade 3 and 4 adverse events included multiple complications and concomitant pathology associated with SCI (gastrointestinal and infectious complications, metabolic disorders, myalgia and muscular-tonic syndrome, etc.), surgical treatment (severe anemia due to intraoperative blood loss) and prolonged bed rest (weight loss, venous thrombosis) (see Table 5). The nature of the relationship of AEs with the cell therapy – almost all registered AEs (417 (99.5 %) were definitely "not related to cell therapy". Only in 2 cases (0.5 %) were the mild AEs identified "possibly related to cell therapy". Both events were short-term subfebrile hyperthermia (less than 38 °C) within 2 hours after cells administration.

In both cases, no medication was required, as hyperthermia regressed on its own. It is obvious that SCI patients often have various infectious complications that lead to episodes of hyperthermia. However, none of the patients showed signs of GVHD. After the observation period, we were also able to analyze the immune responses to the injected cell samples in 5 patients (other patients were unavailable at the time of analysis), and the results were negative in all cases. Thus, the data obtained indicate that allogeneic HUCBCs are safe and well tolerated by SCI patients.

The timing of recovery of patients after SCI or the timing of regenerative therapy is still controversial in the scientific community [23]. The importance of early surgical decompression and stabilization of the spine in patients with SCI has been proven [7, 8]. However, proven optimal timing of cell therapy has not yet been determined. Most patients with SCI showed the most degree of neurological recovery within 6 months after injury, with the highest rate of recovery observed within the first 3 months [5]. As a rule, the functional improvement could develop within 12 months, or longer in some cases.

This was the reason for limiting the observation period to one year. All patients, except one, showed a high degree of recovery during 12 months of observation, with the most dynamics of motor function recovery during the first 6 months. More than half (5 of 9) of the patients included in the study achieved the maximum level of recovery within 6 months after receiving SCI. In the remaining cases (4 of 9), this period was somewhat longer – up to 9 months. No significant changes in the neurological status of patients were detected during the period of 9–12 months from the moment of receiving SCI.

In addition, the study demonstrated high primary efficacy of cell therapy. The open design of the study and the small number of patients included do not allow us to judge with a high degree of reliability the presence of a therapeutic effect. However, the tendency for functional recovery was much higher than previously described. One of the largest meta-analyses of the largest cohort studies by V.A. Lee et al. included 661 patients with SCI at the thoracic level without cell therapy [5].

The authors showed that in 84.5 % of patients with ASIA A, the level of neurological deficit did not change within 12 months from the moment of injury, and only 7.7 % of the patients showed recovery (by 1 point to ASIA B) [5]. While in the present study (SUBSCI I), 56 % of the participants showed recovery by 2 points according to the ASIA scale (3 patients – from A to C, 2 – from B to D; 30 % of the patients showed recovery by 3 points: 1 – from A to D, 2 – from B to E). According to V.A. Lee et al., only 4.6 % of patients with ASIA A reached level D, and none of them showed complete regression of neurological deficit (to ASIA E), in addition, only 2.9 % of patients with ASIA B completely recovered to ASIA E [5].

It can be concluded that the recovery rate after cell therapy in the presented SUBSCI I study was much higher than the literature data. It is especially important to note the possibility of full functional recovery in patients with acute SCI and initial paraplegia who received cell therapy.

The improvement in the motor function of the lower extremities (according to the LEMS scale) also differed significantly – in the presented SUBSCI I study, after cell therapy, an improvement on 50 points was recorded in 2 patients with ASIA B and 25 (or more) points in 6 patients with ASIA A; in the paper of V.A. Lee et al. [5], the improvement without cell therapy was 4.1 and 1.5 points, respectively.

In our study, one female patient from the experimental group did not show any recovery of the motor function

of the lower extremities during the observation period; only partial regression of sensory disorders was noted. After 2 years and 4 months, some improvement was observed – the recovery of the neurological deficit severity to ASIA C and motor function of the lower extremities to 9 LEMS points.

It should be noted that this patient had a severe mechanism of SCI (an unsuccessful somersault on a trampoline), which led to a complete bilateral interlocking dislocation of the Th11 vertebra and severe crushing of the spinal cord. The sensitivity of modern MRI does not always allow differentiating a contusion and a rupture of the spinal cord. Probably, the ineffectiveness of cell therapy in this patient, compared to other participants in the study, was caused by the lack of differentiation of the SCI structure because of limitations of instrumental diagnostic possibilities.

The exact mechanisms of the therapeutic effect of HUCBCs when administered systemically have yet to be determined, but several possible mechanisms have already been proposed in animal experiments. Two controversial opinions regarding cell migration to the site of injury are presented in the literature. According to some authors, HUCBCs introduced into the systemic circulation are capable of migrating to the area of SCI, where they differentiate into nerve cells and promote regeneration of damaged tissue [24].

Other authors believe that the cells are unable to pass through the blood-spinal cord barrier (even damaged as a result of injury) and realize their therapeutic potential by activating neurotrophic, neuroprotective, and paracrine mechanisms. The secreted factors promote plasticity of the injured spinal cord by protecting damaged cells and axons, promoting cell survival in the area surrounding the injury zone (resembling the penumbra zone, a potentially viable area of the "ischemic penumbra" in ischemic stroke), stimulating synaptogenesis, neovascularization, and activation of endogenous tissue-specific progenitor cells [16].

In any case, among the currently available cell technologies for the treatment of SCI, most cell types (such as embryonic stem cells, induced pluripotent stem cells) are limited either in efficacy or safety. The safety of HUCBCs has been proven in numerous preclinical studies and a number of clinical trials in various pathologies. Moreover, the efficacy of systemic cell therapy with HUCBCs is comparable to that of mesenchymal stem cells [25], but HUCBCs do not require autologous use and, accordingly, preliminary cultivation.

Given the proven safety of HUCBCs, their efficacy, and numerous advantages over other stem cell sources, it is clear that their potential for use in the treatment of patients with SCI is highly promising. The results of the phase I SUBSCI study indicate that systemic administration of allogeneic HUCBCs is a safe, easily feasible, and effective treatment for acute contusion SCI.

The limitations of the conducted study are a small sample of patients and an open design of the study. Our scientific group continues its work and plans to conduct the next phase (IIa) of a randomized placebo-controlled study to evaluate the effectiveness of systemic cell therapy in patients with severe contusion SCI in the acute period.

CONCLUSION

The results of the phase I clinical trial SUBSCI (Systemic Umbilical Cord Blood Administration in Patients with Acute Severe Contusion Spinal Cord Injury) suggest that repeated systemic administration of allogeneic cryopreserved banked mononuclear human umbilical cord blood cells, matched by blood group and Rh factor, but without taking into account HLA antigen compatibility, to adult patients with severe contusion spinal cord injury in the acute period and severe neurological deficit (A or B on the scale ASIA) is a safe and easily feasible treatment method. Most patients included in the study showed significant improvement in functional outcomes within 12 months after spinal cord injury, which also indicates the primary effectiveness of the presented method.

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