

# CORD BLOOD CELLS IMPROVE NEUROLOGICAL DEFICIT IN PATIENTS WITH TRAUMATIC, DEGENERATIVE AND MENTAL DISORDERS

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## INTRODUCTION

Several pre-clinical animal studies as well as a small number of clinical investigations suggest that cord blood cells can be used in the treatment of a wide variety of diseases including cardiovascular, orthopedic, endocrine and other disorders including neurological ones. However, most of traditional therapies for stroke, traumatic brain or spinal cord injuries, neurodegenerative diseases, cerebral palsy and some other conditions are not efficient. The use of cord blood cells in regenerative medicine may hold promise of restoring functions affected by pathological process.

The aim of clinical trials (phase I-IIa) organized and sponsored by the largest Russian stem cell bank “CryoCenter, Ltd.” ([www.cryocenter.ru](http://www.cryocenter.ru)) and carried out in a number of clinical centers of Moscow and St.-Petersburg was the pilot investigation of safety and efficacy of intravenous infusion of human cord blood cells in patients with neurodegenerative diseases, cerebral palsy and resistant neurological deficits after severe brain trauma.

## RESULTS

Patient's follow-up for 3-6 and 12 months demonstrated that single or multiple (up to four) intravenous injections of allogeneic, AB0/Rh-identical human umbilical cord blood cells did not cause any adverse effects in adult as well as in juvenile patients. On the contrary, after cell infusions significant improvement of neurological status and/or cognitive functions was observed.

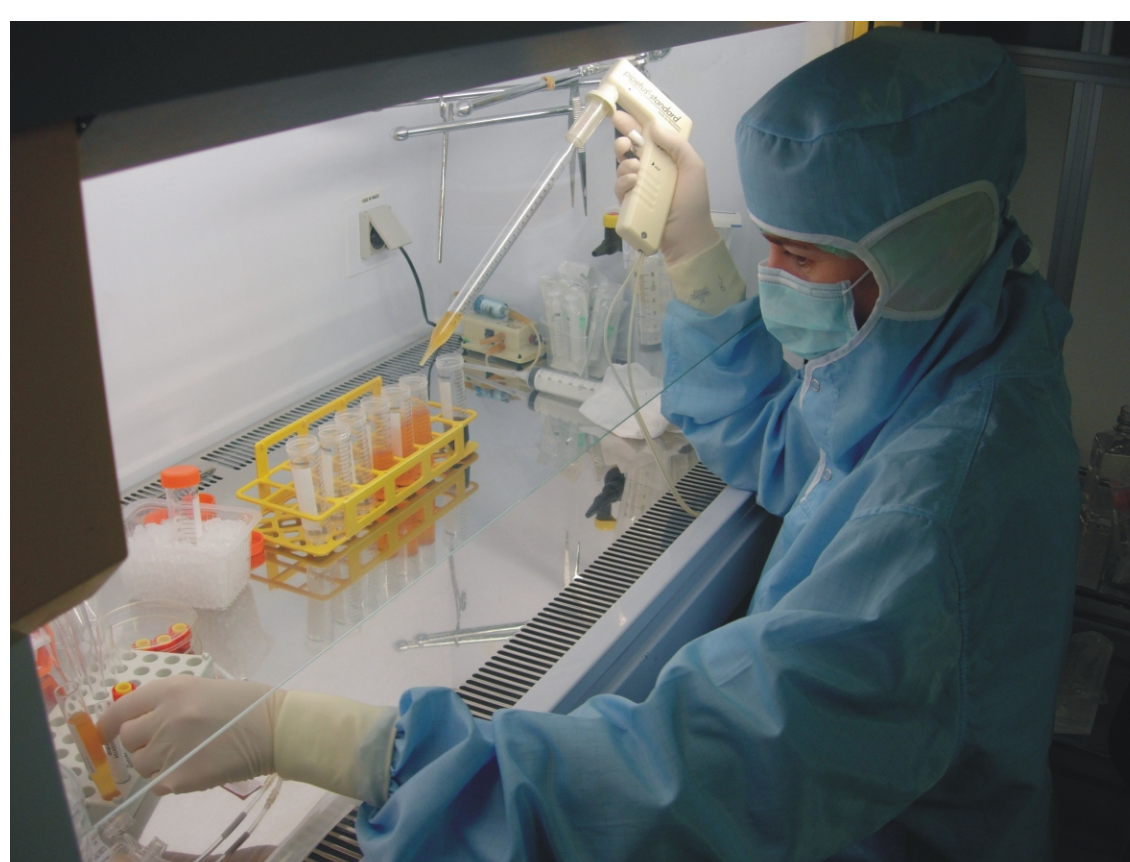
In patients with **posttraumatic encephalopathy** clear tendency for quick (in 3 months) reduction of all asthenic syndrome components (severe fatigue, exhaustion, affective lability, hyperesthesia, signs of vegetative dysfunction and sleepiness) was registered. The level of initiative and mental activity was considerably elevated. Two patients having paresis showed almost full disappearance of symptoms. A considerable language function restoration was seen in patients with aphatic disorders: motor aphasia elements regressed, speech rate increased. Tendency for regression of asthenic symptoms, freelance anxiety level and anxiety somatic symptoms was registered. These data can be interpreted as an improvement of patients psychiatric status. Two patients returned to work.

In patients with **Parkinson's disease** statistically significant improvements were found in several symptoms: rigidity, bradykinesia and functional ability. The functional ability range extension was clearly registered in all patients at the end of the first month.

In patients with **Alzheimer's disease** positive dynamics of cognitive functions (according to Bristol ADL scale) and daily functioning (according to MMSE and ADAS-cog scales) were registered in 2 weeks after cell infusion. According to ADAS-cog and Bristol ADL scales the improvement remained for at least 3 months in 3 patients. Indexes were stabilized on the level of 14th day of the study in 3 cases by MMSE scale. Cognitive and daily functioning improvement was accompanied by restoration of lost hygiene skills and by elevation of daily activity level.

Positive dynamics was registered in a half of all junior patients with spastic form of **cerebral palsy and congenital hydrocephalus**. Spasticity and hyperkinesia diminution was seen in patients. One patient in 2 days after second infusion showed the regression of right sided hemiparesis from 2 to 4 points and decrease in hand clonic seizures frequency. In 4 patients out of 11 (36,3%), in which cerebral palsy or hydrocephalus was combined with epileptic syndrome, frequency of seizers dropped while same anticonvulsive drug dosage was used as before. In 1 patient with congenital amaurosis (*see case report*) restoration of visual function was observed: the boy began to describe objects around him, named objects on the pictures. The control of movements improved. Self-service skills appeared.

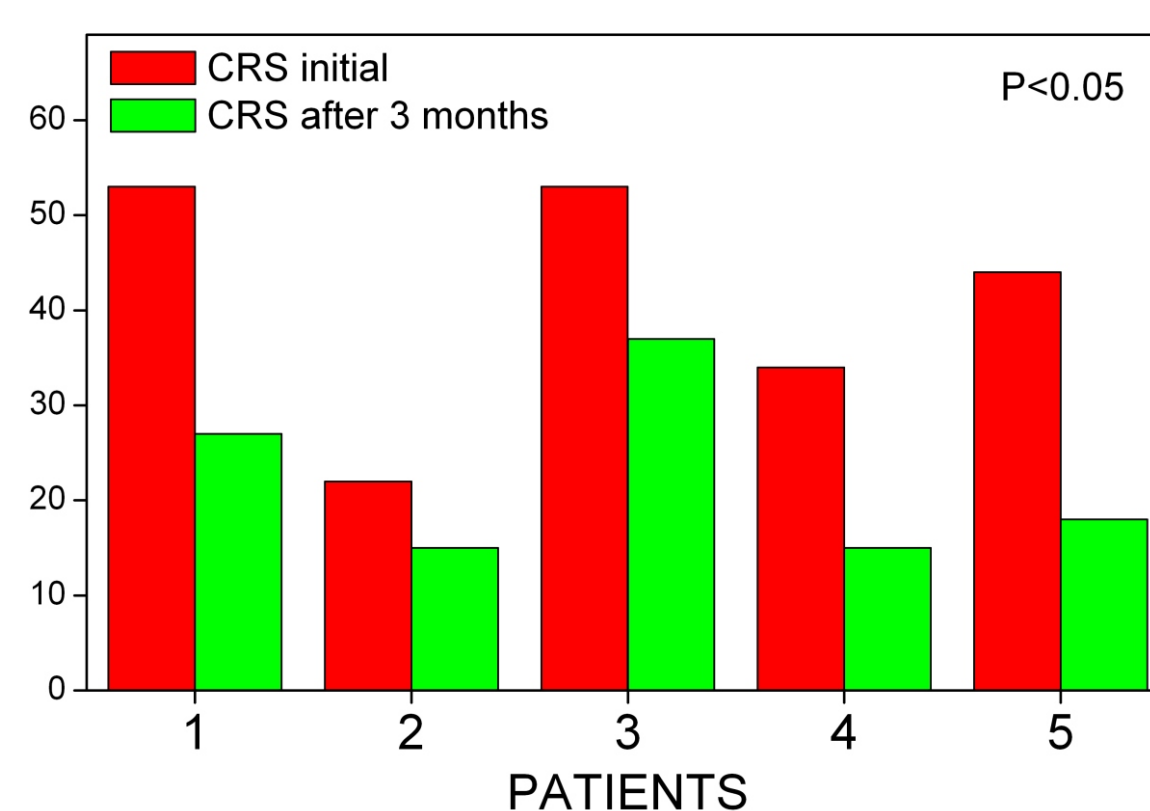
A considerable improvement of several indexes was registered in patients with **schizophrenia** in 6-12 months after 4 cell infusions. Elevation of mental activity, improvement of attention/vigilance (volume, concentration, switching, distribution) and memory (verbal, nonverbal), restoration of learning ability, intensification of executive functions (planning, modeling and mental activity control optimization) were registered.



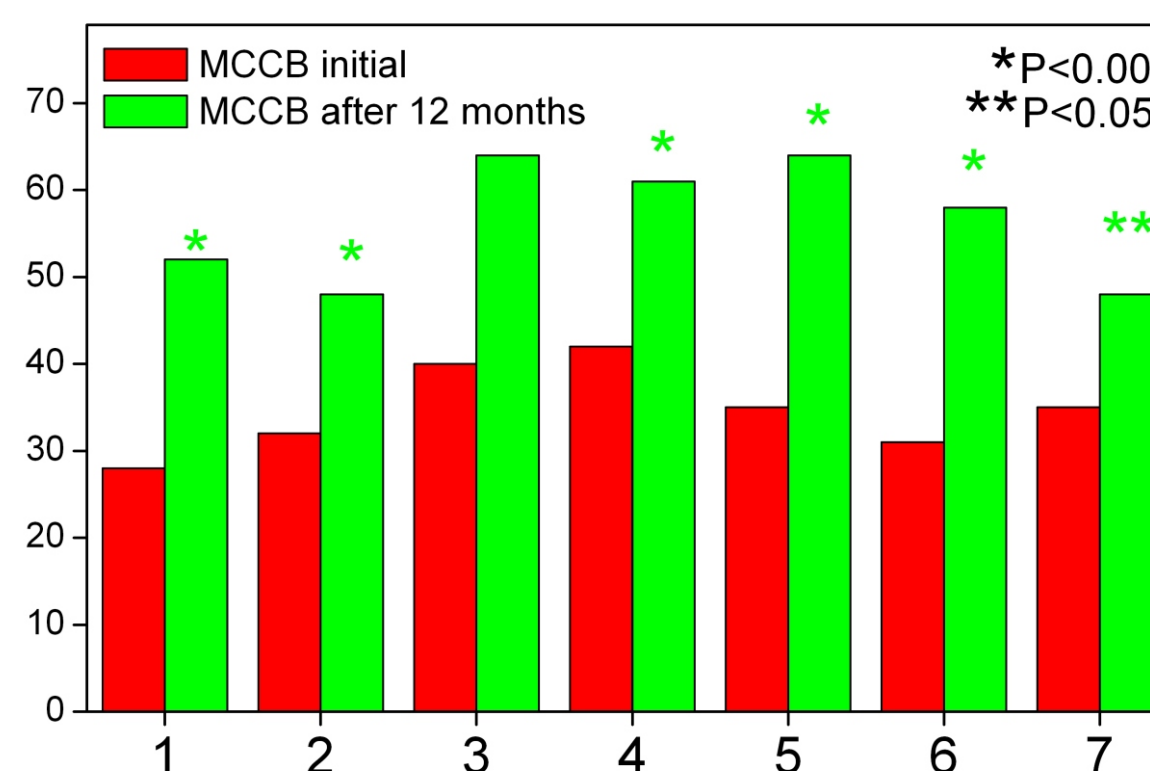
**Therapeutic cells preparation.** After thawing, cells were washed from DMSO and re-suspended in physiological saline containing human serum albumin at amount of about  $250 \times 10^6$  viable cells (therapeutic dose).

## STUDY DESIGN

All clinical protocols were approved by Institutional Review Boards, local and Independent Ethics Committees. After informed consents (in case of under age patients consent was given by parents), patients received 1–4 intravenous infusions of allogeneic, AB0/Rh-identical cord blood cells at the average dose of  $250 \times 10^6$  cells per infusion with 2 weeks intervals (in case of multiple infusions). Standard therapies were preserved in all patients. The list of diseases studied included but was not limited by: posttraumatic encephalopathy (10 patients), Parkinson disease (10 patients), Alzheimer disease (7 patients), cerebral palsy (35 patients), schizophrenia in remission (10 patients). During 1–3–6 and 12 months after manipulations the patients' condition was analyzed by means of battery of special tests and instrumental examinations.



**Figure 1.** CRS dynamics according to summary point value in patients with Parkinson's disease.



**Figure 2.** Comparison of cognitive domains of MCCB in patients with schizophrenia.

1 - speed of processing; 2 - attention vigilance;  
3 - working memory; 4 - verbal learning; 5 - visual learning;  
6 - executive function;  
7 - social cognition

## METHODS

**Cord blood collection, processing and cryopreservation.** Cord blood was obtained after informed consent during full-term normal deliveries from healthy women at the National Center for Obstetrics and Gynecology (Moscow). Blood samples (90-180 ml) were collected in blood-collection bags containing CPDA-1 anticoagulant and processed within 24 hours.

RBC-depleted/plasma-reduced nucleated cells were aseptically isolated by sedimentation, re-suspended in autologous plasma with 10% DMSO, aliquoted in 4 ml cryovials and cooled to -90°C using controlled-rate freezer. During quarantization, all samples were tested for HIV-1/2, hepatitis B and C, HTLV-1/2, HSV-1, CMV, syphilis (sero- and PCR-positive samples were discarded), characterized by AB0/Rh, TNC/CD34<sup>+</sup>-cells count and sterility. Consequently, cells were stored in liquid nitrogen until use.

**Therapeutic cells preparation.** After thawing, cells were washed from DMSO and re-suspended in physiological saline containing human serum albumin at amount of about  $250 \times 10^6$  viable cells (therapeutic dose).

## CASE REPORTS

**Patient R., 21 years old.**

**DS: Posttraumatic encephalopathy with severe asthenic syndrome, speech dysfunction and focal neurological symptoms.**

As a result of a car accident the patient got a brain contusion and was hospitalized into the resuscitation ward. Coma I condition during next 2 weeks, severe left sided hemiparesis developed. Strong speech dysfunction (in acute period lasting one month emitted only “moo-like” sounds), severe left sided hemiparesis, asthenia and fatigue persisted for more than 1 year. Neuropsychologist: right hemisphere type of cognitive disorder. PET: focal and diffuse glucose metabolism changes in right hemisphere. Patient received one intravenous infusion of cord blood cells ( $250 \times 10^6$ ). In 3 months after the procedure practically full paresis regression in left limbs, speech restoration (speech rate improved, speech flow appeared) were registered. Patient had only mild speech and mnestic disorders. The volume of permanent memory increased, level of asthenic depletion decreased, patient accomplishes doctor's exercises more quickly. Asthenic symptoms disappeared. Now patient is back to work.

**Patient A., 9 years old.**

**DS: Chronic progressive focal Rasmussen encephalitis. Epilepsy with frequent simple partial motor seizures, myoclonic and secondary-generalized seizures, treatment resistant form.**

Patient received two intravenous infusions of cord blood cells ( $250 \times 10^6$  each) with 2 weeks interval. A positive dynamics is registered after the second infusion: right sided hemiparesis decreased to 4 degrees, the girl could rear her arm vertically. The amount of twitches in right arm decreased. The control examination (in 5 months): the patient had standard anticonvulsant therapy, at the time of examination there were no epileptic seizures, the level of hyperkinesia decreased, speech improved. Right sided hemiparesis in the leg regressed to 4 degrees, in the arm to 3 degrees. Positive dynamics on EEG. The quality of life improved (speech is better, the girl is able to take care herself, dances a lot).

**Patient Z., 7 years old.**

**DS: Mixed hydrocephalus. Cerebral palsy. Psychomotor and speech developmental delay. Congenital bilateral amaurosis.**

Complaints: psychomotor and speech developmental retardation, visual acuity is simple photoperception. Patient is able to move around the room only by feel. Can't fix the gaze on any object. Constantly makes circular movements with his head, fussy movements with his hands. Patient received three intravenous infusions of cord blood cells ( $100 \times 10^6$ ,  $250 \times 10^6$  and  $250 \times 10^6$ ) with 2 weeks interval. During observation period (6 months) positive dynamics was registered. Child became more calm, hyperkinesia decreased, began to use complex sentences in his speech. Improvement of visual function was observed (says that he sees sun, sky, is able to name the objects on a picture).

**Patient D., 24 years old.**

**DS: Paranoid schizophrenia, partial remission.**

Acute manifestation with paranoid psychosis and Kandinsky-Clérambault syndrome when the patient was 20 years old, hospitalization to psychiatric clinic. During 6 month follow-up period after the discharge felt fatigue, apathy, melancholy, received maintenance therapy. Returned to the curriculum, but remained withdrawn, hypochondriac, favored himself (“didn't manage the high capacity” as he said). In addition to fixed dose of Risperidone got four intravenous infusions of cord blood cells ( $250 \times 10^6$  each) with 14 days interval. 12 weeks after last procedure: restoration of cognitive parameters – the rate of psychiatric processes, working memory, verbal and visual training and executive functions (all the parameters are on the average statistical level). Mood improvement, fatigue and apathy decreased. Patient was able to “finish the business he began”, to read for several hours and to remember the read.

## CONCLUSIONS

- ☐ Intravenous infusion of AB0/Rh-identical RBC-depleted allogeneic umbilical cord blood cells to patients with above-mentioned neurological and mental diseases is safe.
- ☐ In several groups of patients a considerable cognitive improvement is registered including restoration of some brain programs lost earlier.
- ☐ Observed effects of cord blood cells may be explained by paracrine stimulation resulting in long-lasting cognitive improvement.
- ☐ Further studies are needed to precisely define the regimen of infusions and cell dosages.