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Selective Brain Hypothermia in the Comprehensive Rehabilitation of Patients with Chronic Consciousness Disorders

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Summary

Aim: to evaluate clinical effectiveness of selective hypothermia of cerebral cortex for the recovery of awareness in patients with chronic disorders of consciousness (CDC).

Material and methods. 111 patients with CDC 30 and more days after a cerebral event (ischemic or hemorrhagic stroke, brain injury) were included in the study. Exclusion criteria were anoxic brain injury (sequelae of a prolonged asystole or asphyxia), active sepsis, arrhythmia, baseline hypothermia (body temperature lower than 35.5°C). Experimental group included 60 patients, of them 39 patients were in a vegetative state (VS), 21 patients exhibited patterns of minimally conscious state (MCS). Control group incluted 51 patients, of them 32 patients were in VS and 19 patients were in MCS. Patients in the experimental group received 10 sessions (120 minutes each) of selective brain hypothermia (SBH) during the 14-days follow-up period. Patients of both groups received standard identical neurological treatment and rehabilitation procedures. Patients in the control group did not undergo brain hypothermia. The induction of SBH involved cooling of the whole surface of the craniocerebral area of scalp using special helmets. The temperature of the internal surface of the helmet was 3–7°C. Temperature of the frontal lobes of the cortex was monitored with non-invasive microwave radiothermometry, axillary temperature was also registered. The level of consciousness was evaluated using «Coma Recovery Scale-Revised» (CRS-R) scale.

Results. 120-minutes long SBH session reduced the temperature of the frontal lobes of the cerebral cortex by 2.4–3.1°C with no impact on the axillary temperature. Evaluation using CRS-R revealed improvement in all studied functions (auditory, visual, motor, oromotor, communication, arousal) in patients in the experimental group after 10 SBH sessions. Level of consciousness in patients from the experimental group in VS increased from 4.5±0.33 to 8.7±0.91 points (P<0.001), for patients in MCS from 11.3±1.0 to 18.2±0.70 (P<0.001) points. In the control group, scores of patients in VS rose from 4.3±0.37 to 6.8±0.49 (P<0.001) points with the most significant changes in auditory and visual functions (P<0.001). In the control group of patients in MCS the oromotor function improved (P<0.05), overall CRS-R scores changed insignificantly from 9.1±0.57 to 10.1±0.86 (P<0.1). The best outcome (CRS-R>19 points) was seen in patients from the experimental group [6 in VS (15.4%) and 8 in MCS (31.8%)]. In the control group, the best results did not exceed 10 points for the patents in VS, while 4 patients in MCS (21%) reached 12–16 scores. During 30-day follow-up period of hospitalization after the SBH sessions mortality rate was 10% (6 patients) in the experimental group and 21.6% (11 patients) in the control group.

Conclusion. Patients with CDC could benefit from serial SBH sessions performed as a part of comprehensive treatment and rehabilitation strategy. We suggest that selective reduction of frontal lobe temperature improves neurogenesis, neuronal regeneration, and neuroplasticity.

Keywords: hypothermia; frontal lobes; chronic disorders of consciousness; neuroprotection; heat shock proteins; cold shock proteins

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Significant advances in modern critical and intensive care have produced a significant increase in the number of patients with severe brain damage who evolve from coma to other chronic disorders of consciousness (CDC), which include vegetative state (VS) and minimally conscious state (MCS) of undetermined duration [1–3].

Neurological examination still predominates in the diagnosis of VS or MCS, despite a wide range of available advanced diagnostic methods. Its reliability can be increased by using clinical scores including the Coma Recovery Scale — Revised (CRS-R. 2004) which helps reveal and document the first manifestations of consciousness and differentiate between VS and MCS [4, 5].

To date, no generally accepted guidelines and standards for diagnosis, outcome prediction, therapy and rehabilitation principles for this category of patients have been developed. Understanding of the pathogenetic mechanisms of reduced consciousness in brain damage and its recovery after coma is still lacking [6–8].

The treatment of patients with CDC includes maintenance of vital functions, while the rehabilitation measures are focused on the restoration of central nervous system activity, and the choice of rehabilitation techniques depends on their availability in a particular clinic, the patient's tolerability and their response to the procedures [9, 10]. The use of various pharmacological agents aimed at increasing the level of consciousness does not provide a sustainable positive result, and symptomatic therapy dominates in the treatment and rehabilitation of patients with CDC [11].

The study of endogenous cytoprotection and organ protection mechanisms developing as a generic nonspecific response on exposure to potentially damaging factors has become one of the popular areas of neuroprotection and neurorehabilitation research. In particular, the study of ischemic preconditioning (IP) and controlled hypothermia revealed distinct organoprotective effects inherent in almost all internal organs and the brain [12]. However, IP has not been fully adapted for clinical use, since ischemic tolerance of the organs develops when subterminal intensity (potentially dangerous) ischemia episodes are reproduced, whereas there are no effective ways for reliable assessment of ischemic load.

The high neuroprotective properties of hypothermia, associated with metabolic depression and genomic response of cells to reduced temperatures, make it attractive for clinical use in brain damage. However, current therapeutic hypothermia (TH) techniques in most cases employ general cooling of the patient with a decrease in body temperature to 32–33°C, which associates with various side effects and complications. The use of target temperature management (TTM) in cerebral accidents aims to control fever, but not neuroprotection [13].

Meanwhile, the use of selective cortical hypothermia (SCH) achieved by craniocerebral hypothermia (CCH) could provide reduction of brain surface temperature down to the level of local hypothermia required for the expression of cytoprotective genes. We use the term SCH rather than CCH, as it more accurately reflects the target of hypothermia, which is the hemisphere cortex. This cooling technique manages to lower the temperature of the brain surface only, with little effect on the temperature of basal structures and the body [14]. The feasibility of craniocerebral cooling for developing neuroprotection has been clearly demonstrated in experiments and clinical setting [15, 16].

The use of hypothermia, including SCH, involves monitoring the temperature of the tissues being cooled. Recently, the noninvasive measurement of the cortical temperature based on recording the power of brain's own electromagnetic radiation in the UHF range (3–7 GHz) has been introduced in the diagnosis of cerebral damage [17].

Assuming that SCH is capable of lowering the temperature of the hemisphere cortex and triggering neuroprotective response [18], we conducted a pilot study of the effectiveness of this method under cortical temperature monitoring using UHF radiothermometry in patients with CDC.

The aim of the study was to assess the feasibility of clinical use of selective hemisphere cortical hypothermia (SHCH) in patients with chronic disorders of consciousness (CDC).

Material and Methods

The study included 111 patients with CDC. Inclusion criteria were brain conditions following severe focal brain damage (post ischemic or hemorrhagic strokes, severe traumatic brain injury) at least 30–45 days after cerebral accidents and recovery from coma. Exclusion criteria were anoxic brain damage (after prolonged asystole or asphyxia) with widespread diffuse damage to the cerebral cortex, sepsis, cardiac rhythm disorders, baseline hypothermia (body temperature below 35.5°C), terminal illness.

All patients were randomized into two groups. The main group (n=60) included two subgroups. The first subgroup (M1) was composed of the 39 patients in VS (15 women with the mean age 36.7±4.4 years, 24 men with the mean age 43.3±3.4 years). The second subgroup (M2) included 21 patients with MCS minus (7 women with the mean age 44.6±7.7 years and 14 men with the mean age 47.5±3.2 years). The comparison group (n=51) also

included two subgroups. The first subgroup (C1) was composed of of 32 patients in VS (20 women with the mean age 46.9±3.2 years, 12 men with the mean age 44.1±4.1 years). The second subgroup (C2) comprised 19 patients in MCS-minus (10 women with the mean age 56.1±3.5 years and 9 men with the mean age 49.2±3.0 years).

In both groups, the results were recorded on day 1 and 14 of follow-up. After 30 days, mortality was recorded in both groups.

In both groups patients received standard neurotropic therapy and rehabilitation including correction of vital signs, gradual weaning, swallowing correction and removal of tubes, massage, physical therapy, verticalization, myoelectrostimulation, magnetic stimulation, speech therapy, and neuropsychological support.

Patients in the main group received 10 SHCH sessions of 120 minutes duration during the 14-day follow-up period. Patients in the comparison group did not undergo SHCH.

The ATG-01 (Kalashnikov, Russia) therapeutic hypothermia machine was used for the induction of SHCH. The entire surface of the craniocerebral region of the head was cooled using cryoapplicator helmets with the inner temperature of 3–7°C. The cooling procedure was completed by removing the helmet, followed by rapid spontaneous warming of the large hemisphere cortex in the patients. The temperature of the frontal cortex during cooling and the body temperature were monitored.

The cooling modes were chosen empirically based on data from noninvasive UHF radiothermometry of the brain, which allowed monitoring the level of cortical temperature decrease.

UHF radiothermometry of the hemisphere cortex was performed using the RTM-01-RES device (RES LLC, Russia). The device allows to register the power of brain's own electromagnetic radiation at the depth of 4–5 cm from the scalp surface and measure the brain surface temperature in Celcius degrees, as the radiation power is proportional to the intensity of tissue metabolism and its temperature. Measurements were taken in the projection of the left and right frontal lobes using an antenna placed on the scalp directly next to the cooling helmet (Fig. 1). The temperature was measured prior to the procedure and then every 30 min until the end of cooling, immediately after the cooling, and 30 min later. The studies were performed in standard conditions of the intensive care unit (ambient temperature 25–27°C, humidity 75–80%).

The level of consciousness was assessed according to the Coma Recovery Scale-Revised (CRS-R, 2004) with evaluation of auditory, visual, motor, oromotor, communication and arousal functions (in points). CRS-R scale results of the main group patients before the first session and on day 14 after the 10th session were analyzed. In comparison group patients, CRS-R scale data were taken on the day of enrollment and on day 14.

Fig. 1. Temperature measurement.
Note. The antenna is placed over the projection of the left frontal lobe.

The significance of the obtained data was confirmed based on:

- Sufficient sample size for a pilot study (111 patients were divided into the main and comparison groups, each of which had an adequate number of patients allowing for statistical analysis)
- Statistical analysis of results using the SPSS Statistics 21.0 software package. To assess the significance of differences between the groups, the Student's t-test was used, with a prior estimation of distribution of variables for normality. Differences were considered significant at $P \leqslant 0.05$.

Results

Temperature measurements showed that before the first and next procedures, the mean temperature in the projection area of the frontal lobes of the left (LH) and right (RH) hemispheres did not differ (36.4±0.1°C and 36.4±0.1°C, respectively) between the VS and MCS-minus groups. Body temperature was 36.4±0.1°C. After 30 minutes of cooling, the LH and RH temperatures began to drop, and after 90 minutes were 33.9±0.4°C and 33.5±0.5°C, respectively. After removing the cooling helmet from the patient's head, the temperature in the LH and RH was 34.0±0.4°C and 33.3±0.5°C and remained low after 30 minutes post cooling at 35.7±0.1°C and 35.7±0.1°C, respectively. Throughout the cooling period and after the procedure, the body temperature did not alter, remaining within the normal limits (Fig. 2).

The total CRS-R score was 6.9±0.6 in the main group (n=60), 4.5±0.3 in the M1 subgroup (VS, n=39), and 11.3±1.0 in the M2 subgroup (MCS,

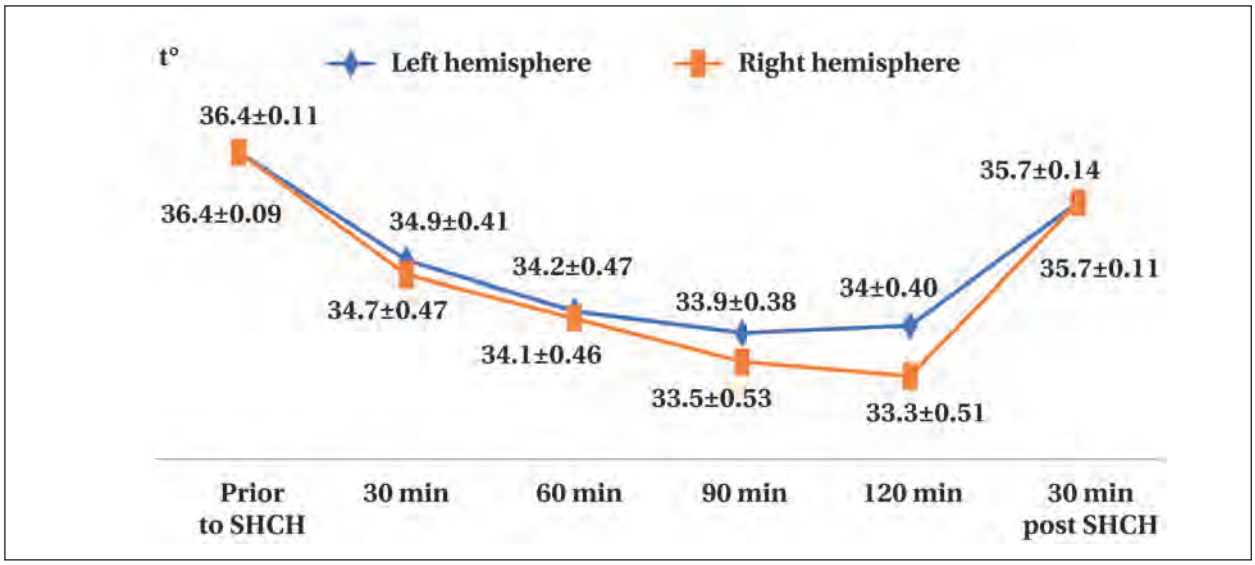

Fig. 2. Evolution of temperature changes in the left and right frontal lobes before and after SHCH.
Note. t° — mean temperature of frontal lobes. 30 min, 60 min, 90 min, 120 min — temperature readings in the frontal lobes at time points during the cooling session.

n=21) on day 1 of the study. The total CRS-R score was 6.1±0.5 in the comparison group (*n*=51), 4.3±0.4 in the C1 subgroup (VS, *n*=32), and 9.1±0.57 in the C2 subgroup (MCS, *n*=19).

On day 14 of the study, after the 10th SHCH procedure, the CRS-R score in the main group was 12.1±0.9, demonstrating a highly significant increase (*P*<0.001). In the comparison group, the CRS-R score on day 14 of the study was 8.1±0.5 which was also significant (*P*<0.05). In the main group, this score reached 8.7±0.91 in the M1 subgroup (*P*<0.001) and 6.8±0.49 in the C1 subgroup also on day 14 (*P*<0.001). In the M1 subgroup, auditory, visual, oromotor, communication, and arousal functions increased most significantly (*P*<0.001), and motor function increased slightly less significantly (*P*<0.005). In the C1 subgroup, only auditory and visual functions increased most significantly (*P*<0.001), while motor, oromotor, and communication functions increased less significantly (*P*<0.005) and the level of arousal function remained unchanged.

The averaged data show that patients in VS who received the SHCH course reached the CMC-minus level, whereas the changes in the CRS-R scale were less evident in the C1 subgroup.

Reflecting the general trend of increasing level of consciousness in patients in both groups and in each subgroup, the average values do not take into account heterogeneity of the results. Thus, in the M1 subgroup, the best results (CRS-R >16 points) were obtained in 6 patients (15.4%): 3 patients reached 16–19 points (MCS-plus), and CRS-R values reached 20–21 points in another 3 patients, indicating their progression to clear consciousness. In the C1 comparison group (SHCH not performed), the best results (CRS-R> 11–13 points), were achieved in 5 patients (15.6%), which corresponds to the CMS-minus level.

Functional assessment using the CRS-R scale in patients of the M2 and C2 on day 1 of the study showed that they were in MCS-minus. On day 14 of the study, after the SHCH course, the CRS-R score for all studied functions in the M2 subgroup demonstrated significant increase reaching 18.2±0.7 points (*P*<0.001). Patients in the comparison group (C2 subgroup) also showed an increase of oromotor function on day 14 of follow-up (*P*<0.05), but the mean increase of CRS-R score to 10.1±0.86 points was not significant (*P*>0.1).

Heterogeneity of results after 14 days was observed in both subgroups of the main group and the comparison group. In the main group, in the M2 subgroup, the best results (CRS-R > 16 points, MCS-plus) were obtained in 8 patients (38.1%), and in 5 patients in this group, CRS-R values reached 20–23 points, indicating a significant recovery of consciousness. In C2 comparison group (no CRS-R was assessed), 4 patients (21%) achieved a CRS-R score of 12–16 on day 14, which corresponded to MCS-plus.

The functional changes on the CRS-R scale in patients of the main and comparison subgroups are shown in the table below.

Analysis of mortality after 30 days showed that in the main group 6 patients of the M1 subgroup died (15.4%). In the M2 subgroup, all patients were alive. In the comparison group, 7 patients died in the C1 subgroup (21.9%) and 4 patients died in the

The functional changes on the CRS-R scale in patients of the main and comparison subgroups

Functions according to CRS-R	Parameter values in groups							
	Main (SHCH)				Comparison			
	M1		M2		C1		C2	
	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
Auditory	0.7±0.10	1.5±0.18***	2.2±0.23	3.3±0.12***	0.7±0.11	1.3±0.11***	1.6±0.16	1.5±0.19
Visual	0.8±0.11	1.9±0.23***	2.6±0.31	4.1±0.22***	0.8±0.10	1.3±0.10***	1.8±0.16	2.1±0.21
Motor	1.3±0.13	2.1±0.24**	3.1±0.31	4.8±0.19***	1.2±0.15	1.7±0.11**	2.3±0.18	2.4±0.27
Oromotor	0.4±0.09	0.9±0.13***	0.8±0.15	1.8±0.17***	0.2±0.07	0.6±0.12**	0.7±0.15	1.1±0.17*
Communication	0.1±0.04	0.6±0.11***	0.6±0.15	1.5±0.11***	0.2±0.07	0.5±0.12**	0.9±0.15	1.0±0.20
Arousal	1.3±0.11	1.8±0.14***	2.1±0.16	2.8±0.12***	1.3±0.12	1.5±0.13	1.8±0.16	2.0±0.13
Total	4.5±0.33	8.7±0.91***	11.3±1.0	18.2±0.70***	4.3±0.37	6.8±0.49***	9.1±0.57	10.1±0.86

Note. * — $P \leqslant 0{,}05$; ** — $P \leqslant 0{,}01$; *** — $P \leqslant 0{,}001$. The M1 and C1 patients were in vegetative state, the M2 and C2 patients were in minimally conscious state.

C2 subgroup (21.1%). A total of 6 patients (10%) died in the main group and 11 patients (21.6%) in the comparison group. The main causes of death in both groups were infections, thromboembolic complications, multiple organ failure.

No complications or side effects of SHCH were registered, and the patients tolerated the procedures well.

Discussion

The mechanisms of neuroprotective effects of hypothermia during the acute period of brain disorders have been extensively studied [19–21]. They include metabolic reactions such as limited consumption of oxygen and substrate, inhibited excitotoxicity reactions and receptor-mediated interactions of signaling molecules, control of edema and inflammatory response, apoptosis, etc. Meanwhile, the temperature signal appearing within the range of 2–3°C variation is sufficient for the expression of genes encoding a wide array of different stress-protecting proteins.

The expression of early genes c-fos and c-jun has been shown to develop when decreasing temperature in cortical neuronal culture leads to accumulation of various cold shock proteins (CSPs) [22]. Temperature fluctuations within 1–3°C are sufficient for expression of genes encoding the synthesis of heat shock proteins (HSPs). However, temperature increase promotes a decrease in HSP production, while warming induces an increase in their production even at lower temperatures (below 32°C). These data were confirmed in many experimental studies [23].

HSPs and CSPs are reasonably considered to be stress proteins with a high potential of neuroprotection, and the initiation of their production is associated not only with temperature signal, but also with exposure to other potentially dangerous stimuli [24]. The studied class of stress-proteins promoting neuroprotection and activating neuroregeneration and neuroplasticity is quite extensive [25, 26]. Importantly, the effects of early gene expression persist for up to several days.

The above-mentioned prerequisites allowed assuming that a course of daily SHCH procedures providing a 2.5–3°C reduction in the brain surface temperature can result in the accumulation of stress proteins, which, theoretically, can have a positive effect on the recovery of consciousness in patients with CDC. These assumptions have been supported, to a certain extent, by the results of clinical studies.

Use of a hypothermic effect on the brain in patients with CDC resulting from severe brain damage and manifesting as VS and MCS-minus does not seem to be as self-evident as in acute brain conditions. However, it is necessary to keep in mind that the completed damage pattern seems to be mostly applicable for the destructive events which had already occurred and cannot be corrected. Meanwhile, the patients with CDC still retain a certain rehabilitative potential which determines the outcome of the disease. The rehabilitation strategy in these cases is aimed at using methods activating body's own resources and increasing the rehabilitation potential. The latter include various neuromodulation methods such as transcranial magnetic and electrical stimulation, as well as SHCH. In particular, a 120-minute cooling period has been shown to provide a 15–20% decrease in the linear blood flow rate in the major cerebral vessels (anterior, middle and posterior cerebral arteries), and during the warming period the blood flow rates quickly return to their initial values [15]. That is, a period of non-hazardous hypoperfusion develops when the temperature decreases, and reperfusion initiates upon warming. Active radicals, as well as the temperature reduction itself, become a powerful trigger for the expression of early genes encoding stress proteins, which could prevent the progression of destructive processes and increase the potential of intact brain areas.

These hypotheses are rather speculative, but the results of our pilot study demonstrate the positive impact of SHCH in patients with CDC, which

emphasizes the feasibility of this approach in an integrated rehabilitation plan. Obviously, further in-depth studies of selective brain hypothermia are needed to improve the effectiveness of therapy and rehabilitation of CDC patients. Determination of molecular markers of brain damage and recovery as well as of the oxidative status seems essential for clarification of mechanisms of the obtained effects.

Conclusion

Our results demonstrate a positive effect of selective brain hemisphere hypothermia on the recovery of consciousness in patients with CDC. The use of SHCH courses in patients with CDC can be recommended as part of an integrated treatment and rehabilitation plan. Selective hypothermia of brain hemispheres could improve neurogenesis, neuroregeneration and neuroplasticity.

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