Article

Correction of Disrupted Circadian Rhythm of Cerebral Temperature in Patients with Chronic Impaired Consciousness after Severe Brain Damage by Using Low-temperature Technologies

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Abstract: Introduction. After emerging from coma, patients with severe brain damage often fall into states of chronic impaired consciousness (CIC) for an indefinite period. An increasement of these patients causes significant social and economic problems. The current strategy of therapy in patients with CIC mainly consists of maintaining vital organs functioning, infection control and nutritional support. To date, there is no sufficient deep understanding of consciousness restoring processes after emerging from coma. Studies of the brain thermal balance in patients with CIC have demonstrated extreme violations of thermal regulation, in particular, the absence of circadian rhythms of body and brain temperature. Development of methods for correcting circadian rhythm disorders may become a key approach aimed at increasing the level of consciousness in these patients. Purpose of the study. To evaluate the influence of selective craniocerebral hypothermia (SCCH) on cerebral temperature circadian rhythms and heterogeneity, as well as the processes of restoring level of consciousness in patients with CIC. Materials and methods. 31 patients with CIC were included. All patients underwent the assessment of consciousness and a 2-day circadian rhythms' registration. Patients with impaired cerebral temperature circadian rhythms were randomized into 2 groups: main and control groups. Patients of the main group underwent 10 sessions of SCCH daily in addition to the basic pharmacotherapy and rehabilitation, compared to the control group. After 14 days, results were re-evaluated. Results. Measurements of the cerebral cortex temperature showed statistically indifferent values in the Left hemisphere (LH) and the Right Hemisphere (RH) in both groups. Correlation analysis revealed presence of strong positive bonds between symmetrical areas of the LH and RH. The represented averaged data indicate that patients in VS, who underwent the course of SCCH, reached the level of "MCS-minus", whereas dynamics in the comparison group was less significant. On the 14th day increasement of the cerebral cortex temperature heterogeneity was seen in patients with VS and MCS in comparison before the course of hypothermia. The correlation coefficients variations expanded, a tendency to normalize circadian rhythms compared were seen compared to the control group where changes in circadian rhythms and cerebral temperature heterogeneity were insignificant. Conclusion. Temperature fluctuations lead to Cold Shock Proteins (CSPs) and Hot Shock Proteins (HSPs) production, which are reasonably attributed to stress proteins carrying high neuroprotective potential. Course of daily SCCH sessions, lowers temperature of the brain by 2.5-3.1° C, stimulates accumulation of stress proteins, which can positively affect the processes of restoring consciousness. In this pilot study it was possible to identify a trend justifying the use of low–molecular technologies to correct circadian rhythm disorders.

Keywords: Disrupted cerebral temperature rhythms, chronic impaired consciousness, craniocerebral hypothermia

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1. Introduction

After emerging from coma, patients with severe brain damage often fall into states of chronic impaired consciousness (CIC) for an undefinate period – those include a vegetative state (VS) and a minimally conscious state (MCS). An increasement of these patients causes significant social and economic problems, which are aggravated by insufficient elaboration of diagnosis recommendations, prognosis of outcomes, principles of therapy and rehabilitation. Despite modern research methods, neurological examination by using Coma Recovery Scale - Revised (CRS–R) prevails in

assessing the level of consciousness of these patients, which allows to identify manifestations of consciousness and assess the current state of auditory, visual, motor, speech, communicative functions and to distinguish the VS, MCS and clear consciousness. The strategy of therapy in patients with CIC mainly consists of maintaining vital organs functioning, preventing development of infections and optimizing nutritional support. Priorities in choosing rehabilitation technologies are determined by availability of medical centers and are often based on assumptions of positive impact on processes of brain function. Massage and movement simulators, verticalization, sensory and electrical stimulation, transcranial magnetic stimulation undoubtedly affect positevely the somatic status of patients, but the effectiveness of these technologies in terms of increasing the level of consciousness remains unclear. Studies of the brain thermal balance in patients with CIC have demonstrated extreme violations of thermal regulation, in particular, the absence of circadian rhythms of body and brain temperature [Shevelev OA et al., 2022]. In case of acute brain injuries, the use of cerebral hypothermia has demonstrated a good clinical result, which is based on the mechanisms of metabolic and epigenetic neuroprotection [Shevelev OA et al., 2019]. To date, there is no sufficiently deep understanding of consciousness restoring processes after emerging from coma. Development of methods for correcting circadian rhythm disorders may become a key approach aimed at increasing the level of consciousness in these patients.

2. The purpose of the study

To evaluate the influence of selective craniocerebral hypothermia (SCCH) on cerebral temperature circadian rhythms and heterogeneity, as well as the processes of restoring level of consciousness in patients with CIC.

3. Materials and Methods

31 patients with CIC were included. All patients underwent the assessment of consciousness level according to CRS-R scale and a 2-day circadian rhythms' registration by using a non-invasive radiothermometry. Patients with impaired circadian rhythms of cerebral temperature were randomized into 2 groups: main and control groups. Patients of the main group underwent 10 sessions of SCCH lasting from 23:00 to 01:00 h daily in addition to the basic pharmacotherapy and rehabilitation, compared to the control group. After 14 days, results were re-evaluated.

4. Results

Measurements of the cerebral cortex temperature at the beginning showed statistically indifferent values of temperature in the Left hemisphere (LH=36.39±0.11°C) and the Right Hemisphere (RH= 36,42±0,09°C) in both groups. Correlation analysis evidentiated the presence of strong positive bonds between symmetrical areas of the LH and RH (r=0.86-0.92), which indicated the presence of low level temperature heterogeneity of the cerebral cortex in both groups, despite the fact that the axial temperature was 36.47 ±0.09 °C. Functional analysis assessment of level of consciousness in the main group at the beginning of the study according to CRS-R was 4.53±0.34, and in patients in the control group – 4.34±0.38 points. On the 14th day after the 10th SCCH session the score reached 8.74± 0.92 points ($p<0.001$) in the main group, and reached 6.83± 0.49 points ($p<0.001$) in the control group. In the main group patients auditory, visual, speech, communicative functions and wakefulness improved most significantly ($p<0.001$), motor function increased somewhat less ($p<0.005$). In the control group only auditory and visual functions increased most significantly ($p<0.001$); motor, speech and communication functions increased less significantly ($p<0.005$), and the level of wakefulness remained unaltered. The represented averaged data indicates that patients in VS, who underwent the course of SCCH, level of "MCS-minus", whereas dynamics in the control group was less significant. On the 14th day, the correlation analysis revealed cerebral cortex temperature heterogeneity increasement in patients with VS and MCS in comparison to start of hypothermia course. The correlation coefficients variations expanded (r=0.36-0.87), which indicated an increase in level of temperature heterogeneity, as well as a tendency to normalize circadian rhythms, compared with the control group, where the correlation coefficients changed insignificantly (r=0.83-0.86) and the circadian rhythms of the cerebral temperature remained disrupted.

4. Discussion

The explanation of positive dynamics under the hypothermic effects on the brain is associated with the modeling of physiologically similar initiation of metabolically conditioned reactions developing with fall of cerebral temperature at bathyphase (at 04:00) thereby triggering reduction of oxygen consumption, inhibition of excitotoxicity reactions and receptor-mediated interactions of signaling molecules, limiting the inflammatory response and apoptosis. In addition, the temperature signal within a small range of variation (1-3° C) is sufficient for expression of genes encoding

stress-protective proteins, including cold shock (CSPs) and heat shock proteins (HSPs). Temperature increment leads to fall of CSPs production, whereas rewarming induces increment of HSPs production. CSPs and HSPs proteins are reasonably attributed to stress proteins carrying high neuroprotective potential. These factors suggest that the course of daily SCCH sessions, lowers temperature of the brain by 2.5-3.1° C, stimulates accumulation of stress proteins, which can positively affect the processes of restoring consciousness.

6. Conclusion

To a certain extent, the above assumptions are confirmed by the obtained results. Small sample size is a limitation of this pilot study, though it was possible to identify a trend justifying the use of low–molecular technologies to correct circadian rhythm disorders and restoration of consciousness in patients with CIC.

Application of artificial intelligence:

The article is written without the use of artificial intelligence technologies.

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