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Review

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Remote Ischemic Postconditioning in Case of Traumatic Brain Injury: a Review of Experimental and Clinical Studies

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RELEVANCE Traumatic brain injury (TBI) remains one of the leading causes of morbidity and mortality worldwide. Despite advances in treatment based on understanding of the mechanisms of brain injury after TBI, there is a clear need for new therapeutic strategies. Remote ischemic postconditioning (RIPostC) can be considered as a non-pharmacological technique to reduce secondary brain damage and improve clinical outcomes in patients with TBI.

AIM OF STUDY Raising awareness of emergency physicians, neurosurgeons, neurologists, neurophysiologists about the possible use of the concept of RIPostC in patients with TBI.

MATERIAL AND METHODS To achieve this goal, the results of clinical and experimental studies of the use of RIPostC after TBI were analyzed. Literature search was carried out in electronic search systems PubMed (https://pubmed.ncbi.nlm.nih.gov), eLibrary (https://elibrary.ru) using the keywords: "traumatic brain injury", "remote ischemic conditioning". A systematic search and selection of publications was performed in January–February 2023. The results of the review included patients with an established diagnosis of traumatic brain injury, followed by the use of RIPostC and animals with experimental modeling of TBI in various ways, followed by RIPostC.

CONCLUSION The totality of data suggests that the use of the concept of RIPostC as a non-invasive protective technique in the provision of emergency care for patients with TBI may contribute to limiting secondary brain damage. However, the underlying neuroprotective processes are quite complex and need further study. Establishing the relationship of humoral, neurogenic and inflammatory reactions in response to the use of RIPostC in TBI will contribute to understanding the mechanisms of emerging neuroprotection, help ease the course of the disease and improve the clinical outcome.

Keywords: remote ischemic postconditioning, neuroprotection, traumatic brain injury

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ACTA1 – skeletal muscle α-actin
BP – blood pressure
GCS – Glasgow Coma Scale
GOS – Glasgow Outcome Scale
IL – interleukin
NSE – neuron-specific enolase
RIPostC – remote ischemic postconditioning
S100B – calcium binding protein
SOD – superoxide dismutase
TBI – traumatic brain injury
TNF-α – tumor necrosis factor-alpha

INTRODUCTION

Traumatic brain injury (TBI) is one of the five leading causes of death and disability worldwide [1]. Traditionally, in the pathogenesis of TBI, the stage of primary damage is distinguished with the formation of a contusion area in the form of damage to the parenchyma, disruption of hemo- and cerebrospinal fluid circulation, and often with hemorrhages of varying severity - from diapedesis to hematomas. Pathological changes in brain tissue that are triggered by the injury and develop subsequently are called secondary, caused by a cascade of complex biochemical, metabolic and cellular processes [2]. Patients who survive TBI subsequently suffer from progressive cognitive impairment and neurodegenerative diseases [3]. Severe TBI can induce inflammatory processes and multiple organ failure [4].

The basis of any treatment for TBI is the preservation of neural tissue by restoring blood flow and limiting the processes that support neuronal death and dysfunction. Current emergency care for TBI is associated with rapid restoration of cerebral perfusion against the background of normalization of intracranial pressure, freedom of cerebrospinal fluid spaces and unimpeded cerebral circulation [5]. However, when cerebral perfusion is restored after compression-ischemic events against the background of edema and swelling of brain tissue, reperfusion damage inevitably develops, which can cause additional cell death in the brain matter and significantly affect the unfavorable outcome [6]. While primary brain damage is irreversible, secondary damage is potentially preventable, reversible, and can be minimized [7]. In this regard, the treatment strategy for TBI is aimed at minimizing or preventing secondary brain damage.

Over the past few decades, numerous pharmacological agents have been investigated in an attempt to influence these secondary processes, but currently there are no proven neuroprotective drugs that improve neurological outcome after TBI [8]. In this connection, the development of new therapeutic concepts and innovative methodological approaches to limiting brain damage in TBI is extremely relevant. A modern alternative treatment strategy may involve activating typical endogenous defense mechanisms that are evolutionarily inherent in the body, including adaptive reactions triggered by the brain in response to stress. These mechanisms include ischemic conditioning, which is based on the activation and enhancement of endogenous tissue protection when exposed to short sublethal periods of ischemia and subsequent reperfusion. Such exposure to discrete ischemia contributes to the formation of tissue resistance to more severe ischemic damage [9, 10]. Ischemic conditioning is classified in relation to the period of its formation during the creation of damage by ischemia-reperfusion, and the organ to which the protective effect is directed. Preconditioning is performed before injurious ischemia and can be used as a protective effect in case of impending damage. Preconditioning is used during the ischemia phase before the reperfusion phase. Postconditioning is performed after ischemic injury and can provide protection during the period of reperfusion [11]. Conditioning can be local, that is, performed directly in one organ, or remote, in which normal tissues are subjected to short cycles of ischemia and reperfusion, which helps reduce the effects of ischemia-reperfusion injury at a remotely damaged site. The exact mechanisms that result in the protective response under different conditioning options remain unclear. It is assumed that the mechanisms of humoral, neurogenic regulation and systemic inflammatory response are involved in the implementation of the effects of remote ischemic conditioning [12].

Remote ischemic postconditioning (RIPostC) of the brain is the process of forming a global neuroprotective effect for the brain exposed to damaging ischemia, followed by short episodes of ischemia and reperfusion during the reperfusion period in remote areas of the body (usually in one limb). Brief ischemic stimuli to the limb activate multiple signaling pathways. Remote transmission of signals from the limbs to the brain can occur through circulating biochemical factors, immune cells and/or as a result of stimulation of the

autonomic nervous system [13]. The concept of limb RIPostC was first demonstrated in 1997 on rats to provide cardioprotection [14]. In clinical practice, the protective effect of RIPostC was first shown in 2006 when used after myocardial infarction [15].

In numerous experimental studies on different models of ischemia-reperfusion injury to the brain, the neuroprotective effect was proven histologically and functionally when using both remote and local ischemic postconditioning [16–22]. In clinical practice, the neuroprotective effectiveness of the RIPostC strategy was shown in patients with acute ischemic stroke in the Remote Ischemic Conditioning After Stroke (RECAST) and RECAST-2 trials in 2017 and 2019 [23, 24]. However, there are clinical studies in which the effectiveness of RIPostC was not established [13], which may be explained by the heterogeneity of the study group of stroke patients, as well as the postconditioning protocol used. Currently, many clinical studies on the use of RIPostC for ischemic and hemorrhagic strokes, against the background of stenosis of the middle cerebral or carotid arteries with damage to the spinal cord, are in the continuation stage (RESIST, RECAST-3, REVISE-2, etc.) [13]. Despite different primary pathologies, cerebral ischemia and secondary injury in TBI share common processes, including inflammation, oxidative stress, and blood-brain barrier permeability [25, 26]. Therefore, RIPostC can be considered as a promising therapeutic strategy aimed at limiting the formation of secondary damage in TBI.

Aim of the study: to increase awareness among emergency physicians, neurosurgeons, neurologists and neurophysiologists about the possible use of the RIPostC concept in patients with TBI.

A review of the literature devoted to the study of the use of RIPostC after TBI in clinical practice and in experiments on animals will help decipher the mechanisms of the neuroprotective effect, and provide new information for future fundamental and clinical research with a view to the subsequent possible implementation of this technique in the field of emergency medicine.

MATERIAL AND METHODS

The literature search was carried out in PubMed and eLibrary electronic databases without restrictions on the year of publication. The following keywords were used: “remote ischemic conditioning”, “traumatic brain injury”. For analysis, we selected publications that assessed the effectiveness of RIPostC in patients with TBI in clinical practice or in experimental modeling of TBI on animals. Publications were excluded from the analysis if they: 1) were reviews or reports (abstracts) of symposiums; 2) contained unrelated results, impacts or comparisons. The results are presented in narrative form. A meta-analysis of the data was not performed due to the heterogeneity of the studies.

RESULTS AND DISCUSSION

A total of 12 publications were found in the initial search. Later on, 5 articles were excluded from consideration after reviewing titles and abstracts. After subsequent full-text checking, 5 publications were selected for analysis, 2 of which presented the results of clinical studies, and 3 presented the results obtained by modeling experimental TBI on small laboratory animals.

APPLICATION OF REMOTE ISCHEMIC POSTCONDITIONING FOR TRAUMATIC BRAIN INJURY IN CLINICAL STUDIES

By the time of writing this review, there have been two clinical studies of RIPostC for TBI, the results of which were published in 2015 and 2021. The trials were carried out with the participation of a small cohort of patients with TBI: in the first research, the comparison groups included 20 people, and in the second - 21 people in each group [25, 27].

Biomarkers of injury are used to assess the severity and monitor the effectiveness of interventions for symptoms and pathology associated with TBI [28]. After severe TBI or suspicion of it, the concentration of calcium-binding protein S100 B, neuron-specific enolase (NSE), ubiquitin C-terminal hydrolase L1 (UCH-L1), glial fibrillary acidic protein (GFAP), interleukin-6 (IL-6), interleukin-10 (IL-10), interferon-gamma (IFN-g),

transforming growth factor-beta (TGF-b), lymphotoxin-alpha, tumor necrosis factor-alpha (TNF-α), and intercellular adhesion molecule type 1 (ICAM-1) increase in the blood serum of the patients [28–30].

At the same time, it is believed that increased IL-10 may play a protective role, since IL-10 is known to limit tissue damage and reduce inflammation by inhibiting the synthesis of TNF-α [31]. It should also be noted that serial sampling of many of the listed biomarkers in the serum of patients with severe TBI revealed different time trajectories, which significantly complicates their use for monitoring treatment and predicting outcomes. Today, it is believed that ideal monitoring biomarker trajectories should correspond to or predict symptoms of developing pathology [32]. It is likely that the most effective tools for monitoring and predicting the course of TBI can be the results of metabolomic and proteomic analyzes [33].

The first results of the clinical use of RIPostC for TBI were obtained in a pilot prospective randomized intervention study [25]. The study included patients with a mean age of 46 years; they were diagnosed with blunt TBI with a severity of 8 or lower on the Glasgow Coma Scale (GCS), and intracranial hemorrhage confirmed by computed tomography. In addition to inpatient treatment, the RIPostC protocol was used, which was previously developed for patients with acute myocardial infarction [34]. RIPostC for patients with TBI was performed using a standard manual cuff for measuring blood pressure (BP). The cuff pressure level was maintained 30 mmHg higher than the patient's systolic BP. Within one hour after the patient with TBI was admitted to the hospital, RIPostC was performed, which lasted 40 minutes and was presented in the form of four occlusion/reperfusion cycles of 5 minutes each. 6 and 24 hours after RIPostC, in patients with TBI a significant decrease in serum levels of S100B and NSE was noted compared to patients with TBI, who did not underwent RIPostC. The authors of the research suggested that the observed decrease in the content of biomarkers of acute neuronal damage is due to the neuroprotective effect of the applied RIPostC [25].

The second clinical trial examining the use of RIPostC was conducted in patients with TBI, the severity of which ranged GCS 3-12, the age of the patients ranged from 14 to 65 years [27]. During the first 6 hours after TBI, in addition to hospital treatment, the patients underwent RIPostC on the upper limb using a standard manual cuff, the pressure level of which was maintained 25 mmHg above the patient's systolic BP. The duration of the RIPostC procedure was 40 minutes and presented in the form of four occlusion/reperfusion cycles of 5 minutes each [19]. The effect of RIPostC on oxidative stress and inflammatory reactions was studied. For prognostic assessment of head injury, the Glasgow Outcome Scale-Extended (GOSE) was used. Acute physiological disorders and chronic functional changes were assessed using the Acute Physiology and Chronic Health Evaluation II (APACHE II) scale; and the severity of brain damage was evaluated using the Marshall classification, based on the results of non-contrast computed tomography. The patients with TBI had a significant increase in serum levels of IL-10 and superoxide dismutase (SOD) at 72 hours and on day 6 after RIPostC compared with data in patients without RIPostC treatment. The authors of the study considered the increase in the levels of these two biomarkers in the blood serum of patients with TBI after RIPostC as a neuroprotective effect of this exposure, based on the fact that IL-10 may have protective properties by inhibiting the synthesis of TNF-a; and acute stroke is accompanied by a decrease in SOD activity in the blood serum [31, 35]. However, in an experimental study, RIPostC performed to the limbs after ischemic gastric injury in rats reduced the damage and was accompanied by a decrease in SOD activity in gastric tissue measured after 6 hours [36]. In patients with TBI with and without RIPostC treatment, there was a decrease in the content of TNF-a in the blood serum after 72 hours and on the 6th day. Moreover, in the RIPostC group, after 72 hours the level of TNF-a in the serum was higher, and after 6 days – lower than in the

patients without RIPostC treatment [27]. TNF-a is a signaling protein (cytokine) involved in systemic inflammation, which is responsible for the development of the acute phase of the reaction, and plays an important role in inflammatory processes through the activation of neutrophils, endothelial cells and granulocytes [37]. It is possible that a higher level of TNF-α at a certain time stage of the pathological process after RIPostC treatment for TBI leads to the formation of a neuroprotective effect, as it is known that it can promote the production of nerve growth factor (NGF) [38]. In the RIPostC group, after 28 days the GOSE score was higher, the Marshall scale score improved by days 6 and 28, the physiological state on the APACHE II scale scored lower compared to the patients with TBI, but without RIPostC treatment [27]. It is known that a higher APACHE II score is associated with higher mortality [39].

The published results of clinical studies examining the use of RIPostC for patients with TBI are rare, and much information has not yet been obtained. To answer emerging questions, it is necessary to further conduct larger clinical trials to evaluate the effectiveness of RIPostC, taking into account the gender and age of patients, the severity of TBI, concomitant pathology, and anesthesia. This will allow us to study the safety and effectiveness of this easy-to-implement therapeutic approach to potentially limit secondary injuries from TBI, allowing for its implementation in emergency care.

APPLICATION OF REMOTE ISCHEMIC POSTCONDITIONING FOR TRAUMATIC BRAIN INJURY IN EXPERIMENTAL STUDIES

A brief description of experiments [40–42] devoted to the study of the effect of RIPostC during modeling TBI in animals is presented in the table. All the studies were performed on male mice using two experimental models of TBI (Table). It is known that experimental models of TBI in rodents are divided into four types depending on the method of brain exposure: 1) liquid percussion model; 2) controlled cortical damage; 3) falling weight model; 4) injury caused by a shock wave [43]. The studies examined the effects of RIPostC when administered during early (up to 1 hour) and late reperfusion periods, as well as the effects of prolonged RIPostC after TBI.

The first experimental study examining the neuroprotective effect of RIPostC after TBI was conducted in 2017 on mice [40]. It was shown that RIPostC on the right femoral artery 2 hours after TBI modeling through controlled cortical brain injury helps reduce the number of damaged neurons and astrogliosis in the CA1 field of the hippocampus, cognitive and motor disorders that occur after the trauma (see Table). The researchers also noted a decrease in TNF-α levels in the blood serum of mice in the RIPostC group, suggesting that RIPostC treatment for TBI has an immunomodulatory effect [40]. It was previously shown that the use of RIPostC attenuates inflammatory responses in mice with lipopolysaccharide-induced systemic inflammation [44]. Cognitive functions in the group of mice with TBI and RIPostC treatment improved at 24, 48 and 72 hours, and then at 96 hours of observation there was their significant decrease. Similar observations on persistence of the neuroprotective effect of ischemic conditioning only 24–54 hours after application were noted in patients with aneurysmal subarachnoid hemorrhage [45]. This suggests that the neuroprotective effect of RIPostC treatment decreases over time, and it is likely that longer periods of occlusion/reperfusion or a greater number of cycles could generate a more durable neuroprotective response.

The effects of long-term RIPostC on cognitive and motor functions were studied in a similar mouse model of TBI (see Table) [41]. It was shown that the use of long-term RIPostC, presented in the form of six cycles of hindlimb ischemia/reperfusion for 6 consecutive days after TBI, helps reduce the number of damaged neurons and astrocytes in the CA1 field of the hippocampus and improve cognitive and motor functions within 21 days of observation [41].

Table

Publications selected for analysis of remote ischemic postconditioning (RIPostC) for traumatic brain injury (TBI) in experimental studies

Experimental model parameters			Tests		Effect		Publications
Species Strain Gender Age	TBI model	RIPostC protocol	Functional tests	Organ (tissue)	Biochemical morphological	Functional	
Mice C57BL/6							

studies have shown that in patients with TBI, the level of IGF-1 in the blood serum decreases, and its exogenous increase promotes the survival of neurons after the injury [47]. It should be noted that in the research conducted, when studying the effect of RIPostC in TBI, changes in the levels of protein and metabolites in the blood plasma of mice were shown, while the neuroprotective effect of the applied postconditioning protocol was not functionally or histologically demonstrated.

Further experiments involving animals of different species, strains, ages and sexes using histological and functional criteria for assessing the neuroprotective effect of various models of TBI and RIPostC protocols, as well as analysis methods, including technologies related to research in the field of proteomics, metabolomics and transcriptomics, will allow researchers to identify circulating molecular and biochemical factors, and understand their role in the exchange of information from the limb to the brain during the formation of protection.

CONCLUSION

The number of clinical and experimental studies of remote ischemic postconditioning in traumatic brain injury today is small; however, based on the experience and knowledge already gained, the planning of future experimental and clinical research can be developed and optimized. The mechanisms underlying the formation of the neuroprotective response are complex and require further investigation. The most promising direction in their search is associated with establishing the relationship between systemic inflammatory reactions and humoral and neurogenic regulatory mechanisms in response to the use of remote ischemic postconditioning in traumatic brain injury. The discovered patterns will make it possible to determine optimal dosage regimens, and the possible frequency of use of discrete ischemic stimuli to achieve a positive protective effect. Moreover, knowledge of these protective mechanisms will help create a drug version of neuroprotective therapy that can stop the progression of the pathological process and improve the clinical outcome of traumatic brain injury.

It is obvious that the use of remote ischemic postconditioning in patients with traumatic brain injury has great potential for future inclusion of this technique in the emergency care algorithm for traumatic brain injury in situations where there is no immediate access to specialized medical care, including at the scene of injury. The procedure appears to be easy to learn, does not involve risks, and requires only a compression cuff or tourniquet to briefly restrict blood flow to the extremity; therefore, remote ischemic postconditioning can be used in emergency care at the prehospital stage in order to improve clinical outcomes in patients with traumatic brain injury.

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