ISSN 2304-3415, Russian Open Medical Journal
2025. Volume 14. Issue 1 (March). Article CID e0106
DOI: 10.15275/rusomj.2025.0106

Original article

Neuroprotective effect of remote ischemic preconditioning in MRI-guided focused ultrasound treatment

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Received 18 August 2024, Revised 31 October 2024, Accepted 29 November 2024

Abstract: *Introduction* — Magnetic resonance imaging-guided focused ultrasound (MRgFUS) is used for ablation of various solid tumors and treatment of neurological diseases. During ablation, brain tissue is injured, resulting in the formation of necrosis and edema zones. Therefore, strategies to minimize brain damage are highly relevant**.** The goal of our research was to study the neuroprotective effect of remote ischemic preconditioning (RIPC) in the treatment of movement disorders using MRgFUS.
Material and Methods — The study design was blinded randomized controlled 2-group trial. Patients were randomly assigned to the IPC group (systolic blood pressure +50 mm Hg, n=42) or sham IPC (sIPC) group (diastolic pressure, n=39) prior to MRgFUS in the mode of 3 cycles of 5 min of preconditioning on the forearm with 5 min of rest between cycles.
Results — Following MRgFUS ablation of the ventralis intermediate (VIM) nucleus (gray matter), no differences in lesion size or tremor severity were detected after 2 h between the IPC and sIPC groups. When affecting the pallidothalamic tract (PTT, white matter), in the IPC group, in contrast to the sIPC, the main sizes of the necrotic lesion were significantly smaller after 2 h (frontal dimension, p=0.001; vertical dimension, p=0.037; necrosis lesion volume, p=0.007). Also, after 24 h in the IPC group, the dimensions of the lesion in the PTT were smaller (frontal dimension, p<0.001; vertical dimension, p=0.021; lesion volume, p=0.001).
Conclusion — RIPC preceding MRgFUS has a neuroprotective effect on PTT (white matter).

Keywords: magnetic resonance imaging-guided focused ultrasound (MRgFUS), remote ischemic preconditioning, sham procedure, ablation, neuroprotection, PTT.

Cite as Mukhamadeeva NR, Kachemaeva OV, Lakman IA, Buzaev IV, Galimova RM, Popova TA, Samorodov AV Zagidullin NSh. Neuroprotective effect of remote ischemic preconditioning in MRI-guided focused ultrasound treatment. *Russian Open Medical Journal* 2025; 14: e0106.

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Introduction

These days, image-guided therapy (IGT) is becoming an increasingly promising tool in medicine that integrate ultrasound imaging, magnetic resonance imaging (MRI), computed tomography (CT), radiography and positron emission tomography (PET) with surgery and internal medicine [1, 2]. Treatment evaluation with an adequate imaging protocol is important as a clinical predictor of outcome [3]. The integration of imaging modalities into focused ultrasound (FUS) systems allows for accurate temperature monitoring and treatment planning, thereby improving the safety and efficacy of treatment [4]. MRI-guided FUS (MRgFUS) has received regulatory approval worldwide for the ablation of various solid tumors, treatment of neurological diseases and palliative care of bone metastases. The mechanical and thermal effects of FUS provide the possibility of histotripsy, supportive radiotherapy and targeted drug delivery [5, 6]. However, electromagnetic and radio waves cannot be focused as precisely as ultrasound waves, and their penetration depth is limited. FUS provides tissue penetration in the range from 1 to 20 cm, with a controlled focal spot. The ablation area in this case includes distinct concentric zones: a central necrotic core, surrounding cytotoxic edema, and a larger ring of vasogenic edema [7].

In the context of these treatment methods, of particular interest is the search for, and implementation of, additional methods of tissue protection that ensure the achievement of an optimal therapeutic effect with minimal damage. Ischemic preconditioning (IPC) can become such a method: an experimental phenomenon in which a short-term ischemic stimulus provides protection from a subsequent damaging ischemic event [8]. A number of clinical studies of IPC demonstrate improvement in perfusion parameters of the ischemic area, prognosis in patients with stroke, and a decrease in the frequency of relapses of cardiovascular and cerebrovascular diseases [9, 10].

The goal of our study was to investigate the possible neuroprotective effect of remote IPC (RIPC) in the treatment of movement disorders using the MRgFUS method.

Material and Methods

Patients

The study included patients with movement disorders – Parkinson's disease (PD), essential tremor (ET), cervical dystonia (CD), and anoxic encephalopathy (AE) – who were referred for MRgFUS treatment.

A total of 81 patients with a clinically verified diagnosis were enrolled in the study: 59 men and 22 women. Their median age was 62 years (ranging from 53 to 67 years). The prevailing nosology in the examined sample was PD (61 patients or 75.3%), ET was detected in 14 patients (17.3%), CD and AE were diagnosed in 5 patients (6.2%) and 1 patient (1.2%), respectively. The median duration of the disease was 7 years (ranging from 5 to 12 years).

For the subsequent study, patients were randomized into two groups: the IPC group with 42 patients and sham IPC group (sIPC) with 39 patients. The IPC and sIPC groups were similar in terms of gender and age: 63.5 (53.25; 67.75) years vs. 59 (53.5; 66) years (p=0.268), body mass index (BMI), duration of the underlying disease, concomitant somatic pathology and pharmacotherapy (*Table 1*).

Inclusion and exclusion criteria for the study

The inclusion criteria for the study were:

i) Established clinical diagnosis (in patients with PD, Hoehn and Yahr stage ≥2);
ii) Age over 18 years;
iii) Proven lack of efficacy of pharmacotherapy or other treatment options (in PD patients, no response to levodopa-containing medications at doses exceeding 500 mg per day; in the akinetic-rigid subtype of PD, motor fluctuations despite optimal levodopa therapy; in patients with ET, pharmacotherapy with topiramate and propranolol for more than three months without satisfactory results; in patients with CD, unsatisfactory response to botulinum toxin therapy and a negative test for levodopa treatment; in the patient with AE, unsatisfactory effect from maximum tolerated doses of valproic acid, pregabalin, levetiracetam, tetrabenazine, and levodopa);
iv) Informed voluntary consent to the study.

The exclusion criteria were as follows:

i) Severe somatic pathology, including acute diseases and injuries;
ii) Standard contraindications for MRI such as implanted metal devices incompatible with MRI (including pacemakers) and claustrophobia;
iii) Pregnancy;
iv) Alcohol and substance abuse;
v) Overall skull density ratio of 0.35 (± 0.05) or less according to CT data.

Randomization procedure

The random assignment of patients to IPC or sIPC groups was performed by the sealed envelope method. During IPC, 5-minute cycles of compression of the right forearm with a mechanical tonometer cuff and 5-minute reperfusion cycles were performed. In IPC group, the pressure in the cuff was increased to a level of 50 mm Hg above the actual systolic blood pressure (BP). In sIPC group, it corresponded to the diastolic BP. The procedure was performed no later than 1 hour before MRgFUS.

Methodology of focused ultrasound therapy under magnetic resonance imaging control (MRgFUS)

Pre-procedural imaging included non-contrast CT of the brain using GE, Siemens, and Toshiba devices to calculate the overall skull density ratio and further planning of FUS parameters during surgery. MRgFUS treatment was performed using the ExAblate 4000 device (Insightec v.7.0.404) with 1,024 piezoelectric ultrasonic wave transducers, combined with the GE Optima MR450W 1.5T MR-scanner in several stages. At the first stage, ultrasound was focused at low power for 10-20 seconds, the temperature of impact on the brain tissue was usually 41-46 °C.

After confirming that the device was properly focused on the target using 3D T1-weighted MR images, the FUS energy was gradually increased to achieve a temperature of 46–50 °C in the target area. This ensured a reversible therapeutic effect without causing side effects.

If it was necessary, the exposure parameters were adjusted. The ablation per se was performed with a gradual increase in the total energy due to the intensity or duration of ultrasound exposure parameters up to the temperature of 60 °C in the target. The ablation target was ventralis intermediate (VIM) nucleus of the thalamus or a combination with exposure to the pallidothalamic tract (PTT). The target was localized using standard indirect measurements from the anterior/posterior commissure line of the brain. The patients were fully conscious. During the therapy, the physician monitored their somatic and neurological status, assessed changes in the intensity of symptoms (tremor, rigidity, etc.). Postoperative monitoring was carried out after 2 and 24 h: a control T2 weighted MRI of the brain was performed in the frontal, sagittal and vertical projections with a slice thickness of 2 mm. The sizes of the necrosis and edema at the sites of FUS impact were determined.

Statistical data processing

The R 4.1.1 for Windows was used to analyze the obtained data. At the first stage, descriptive statistics were calculated to characterize the groups by continuous variables, including the median (Me) and quartiles (Q1, Q3), as well as by frequency variables, including the absolute frequency of occurrence and the proportion (%). To assess intergroup differences between the sIPC and IPC groups, the Mann-Whitney U test was employed for numerical continuous variables, while the chi-squared test was conducted for categorical variables (including the Yates's correction for continuity in the case of the absence or extremely rare frequency of occurrence of a feature in one of the study groups). At the second stage, we used the nonparametric Wilcoxon test for dependent samples for intragroup comparisons of the variables 2 and 24 h after MRgFUS. Differences were considered statistically significant at $p \leq 0.05$.

Table 1. Comparison of parameter values between IPC and sIPC groups

Parameter	*Count (%) or Me (Q1; Q3)*		*Differences according to the χ2 test (categorical variables: χ2 statistics, p-value) and the Mann-Whitney U test (quantitative variables: Z statistic, p-value)*
	IPC group (n=42)	sIPC group (n=39)	
Male sex	31 (73.8 %)	28 (71.8 %)	χ2 =0.041; p=0.839
Age, years	63.5 (53.25; 67.75)	59 (53.5; 66)	Z=1.107; p=0.268
Body mass index, kg/m^2	25.05 (24; 29.225)	25 (24; 25.3)	Z=0.989; p=0.322
Duration of the underlying disease, years	7 (4; 20)	7 (5; 10)	Z=0.569; p=0.869
Hypertension	25 (59.5%)	16 (41%)	χ2=2.768; p=0.97
Coronary artery disease	4 (9.5%)	4 (10.3%)	χ2=0.012; p=0.913
Diabetes mellitus	5 (11.9%)	2 (5.1%)	χ2=0.474; p=0.491#

Yates's correction was used for χ^2 test; IPC, ischemic preconditioning; sIPC, sham ischemic preconditioning.

Table 2. Comparison of parameter values between IPC and sIPC groups 2 h after MRgFUS

Variable	*Me (median); Q1; Q3 (interquartile range)*		*Differences according to the Mann-Whitney U test, Z statistic, p-value*
	IPC group (n=42)	sIPC group (n=39)	
Frontal dimension of necrosis focus (VIM nucleus), mm	4.44 (3.45; 5.07)	4.65 (4.1; 6)	Z=-0.1401; p=0.102
Sagittal dimension of necrosis focus (VIM nucleus), mm	5.31 (4.43; 6.56)	5.25 (4.26; 6.3)	Z=0.0248; p=0.426
Vertical dimension of necrosis focus (VIM nucleus), mm	5.39 (4.42; 6.29)	5.3 (4.45; 6.15)	Z=0.0065; p=0.891
Volume of necrosis focus (VIM nucleus), mm^3	68.02 (38.05; 95.9)	68.17 (54.15; 103.52)	Z=-0.6321; p=0.645
Edema size (VIM nucleus), mm	3.53 (2.96; 4)	3 (2.38; 3.81)	Z=0.0384; p=0.111
Volume of necrosis focus + edema (VIM nucleus), mm^3	1,013.3 (539.3; 1363.9)	748.1 (361.1; 1,245.5)	Z=10.426; p=0.284
Edema volume (VIM nucleus), mm^3	940.7 (480.5; 1235.9)	643.9 (302.5; 113.6)	Z=11.058; p=0.251
Frontal dimension of necrosis focus (PTT), mm	3.52 (3.07; 3.8)	5 (3.83; 5.85)	Z=-0.0984; p=0.001**
Sagittal size of necrosis focus (PTT), mm	5.2 (4.73; 5.82)	5.02 (4.5; 6.59)	Z=-0.0085; p=0.941
Vertical size of necrosis focus (PTT), mm	4.42 (4,11; 4.87)	5.45 (4.53; 6.08)	Z=-0.0471; p=0.037*
Volume of necrosis focus (PTT), mm^3	42.71 (30.51; 49.52)	77.37 (58.23; 97.67)	Z=-2.0802; p=0.007**
Edema size (PTT), mm	3.59 (3.05; 4.27)	3 (2; 3.55)	Z=0.0471; p=0.07
Volume of necrosis focus + edema (PTT), mm^3	805.2 (525.4; 1077.8)	772.4 (424.9; 1044.2)	Z=6.0736; p=0.358
Edema volume (PTT), mm^3	762.7 (487.8; 1043.3)	701.1 (353.3; 964.4)	Z=8.1538; p=0.178

*, ** differences between the groups are significant at p<0.05 and p<0.01, respectively; MRgFUS, magnetic resonance imaging-guided focused ultrasound; IPC, ischemic preconditioning; sIPC, sham ischemic preconditioning; VIM, ventralis intermediate; PTT, pallidothalamic tract.

Table 3. Comparison of parameter values between IPC and sIPC groups 24 h after MRgFUS

Variable	*Me (median); Q1; Q3 (interquartile range)*		*Differences according to the Mann-Whitney U test, Z statistic, p-value*
	IPC group (n=42)	sIPC group (n=39)	
Frontal dimension of necrosis focus (VIM nucleus), mm	5.42 (4.57; 6.25)	5.65 (4.78; 6.65)	Z=-0.028; p=0.506
Sagittal dimension of necrosis focus (VIM nucleus), mm	6.58 (5.1; 7.75)	6.38 (5.8; 6.88)	Z=0.0071; p=0.785
Vertical dimension of necrosis focus (VIM nucleus), mm	6.5 (5.11; 6.99)	5.9 (5.28; 7.5)	Z=-0.0178; p=0.814
Volume of necrosis focus (VIM nucleus), mm^3	113.46 (65.12; 181.31)	109.21 (78.81; 160.75)	Z=-0.8228; p=0.841
Edema size (VIM nucleus), mm	4.16 (3.73; 4.66)	4 (3.43; 4.63)	Z=0.0138; p=0.491
Volume of necrosis focus + edema (VIM nucleus), mm^3	1,441.3 (1,052; 2,134.1)	1,599.5 (1,031; 2,069.1)	Z=-0.4535; p=0.875
Edema volume (VIM nucleus), mm^3	1,388.9 (970.4; 1,952.1)	1,455.9 (943.5; 1,960.5)	Z=0.3694; p=0.832
Increase in necrosis volume (VIM nucleus), mm^3	33.09 (18.50; 75.03)	34.77 (9.88; 71.56)	Z=-0.3887; p=0.796
Frontal dimension of necrosis focus (PTT), mm	4.4 (3,92; 5)	5.85 (5.13; 6.8)	Z=-0.1174; p<0.001***
Sagittal dimension of necrosis focus (PTT), mm	5.84 (5.1; 6.15)	5.95 (5.05; 7.29)	Z=-0.0254; p=0.388
Vertical dimension of necrosis focus (PTT), mm	5.13 (4.34; 5.91)	6.15 (5.13; 6.8)	Z=-0.0712; p=0.021*
Volume of necrosis focus (PTT), mm	67.94 (51.15; 88.27)	121.62 (76.21; 160.15)	Z=-4.1027; p=0.001**
Edema size (PTT), mm	4.08 (3.82; 4.45)	3.8 (3.22; 4.76)	Z=0.0128; p=0.406
Volume of necrosis focus + edema (PTT), mm^3	1,299 (1,073; 1487)	1311.4 (950.1; 2196.2)	Z=-23.694; p=0.506
Edema volume (PTT), mm^3	1,213.5 (1007.9; 1424.6)	1224.4 (854.7; 2027.1)	Z=-19.591; p=0.744
Increase in necrosis volume (PTT), mm^3	11.47 (3.13; 41.86)	47.45 (11.16; 69.08)	Z=-2.0225; p=0.039*

*, **, *** differences between the groups are significant at p<0.05, p<0.01 and p<0.001, respectively; MRgFUS, magnetic resonance imaging-guided focused ultrasound; IPC, ischemic preconditioning; sIPC, sham ischemic preconditioning; VIM, ventralis intermediate; PTT, pallidothalamic tract.

Results

During the MRgFUS procedure, successful formation of a thermal necrosis focus in the target areas of the brain was achieved in both groups of patients. Control imaging after MRgFUS did not reveal signs of hemorrhage or unwanted heating of the brain tissue in either group. Comparison of the planar sizes and volumes (V) of necrosis and edema foci on 3D T1 weighted MR images 2 and 24 h after MRgFUS did not reveal a statistically significant difference between the IPC and sIPC groups when the VIM nucleus was targeted. However, during PTT ablation in the IPC group, the frontal and vertical dimensions, and the volumes of necrotic foci 2 and 24 h after surgery were statistically significantly smaller (p<0.05). Moreover, the increase in the volume of necrotic foci after MRgFUS in the IPC group was statistically significantly smaller than in sIPC group (p=0.039) (*Tables 2* and 3).

Intragroup comparison of the dimensions of necrotic foci, as well as edema after 2 and 24 h, and the increase in necrotic volumes in both IPC and sIPC groups according to the Wilcoxon test demonstrated significant differences in most parameters (*Table 4*).

Comparison of the effect on the effectiveness parameters in terms of correction of movement disorders in the IPC and sIPC groups did not show a statistically significant difference; that is, RIPC procedure did not aggravate the outcomes of MRgFUS therapy: the Mann-Whitney U test did not reveal statistically significant reduction (%) of postural tremor (p=0.755), kinetic tremor (p=0.816), and resting tremor (p=0.811).

Discussion

Our study was the first to examine the effect of RIPC on thermal ablation of the VIM nucleus and PTT by MRgFUS, used to treat symptoms of movement disorders.

The study was a randomized controlled trial in two groups: with IPC (systolic pressure +50 mm Hg) and sIPC (diastolic pressure). Both groups were similar in terms of the main clinical and diagnostic parameters (*Table 1*; p>0.05).

As a result of MRgFUS therapy targeting the VIM nucleus (gray matter), no morphological and clinical differences were detected in both groups of patients in terms of the lesion size.

When the PTT tract (white matter) was exposed to MRgFUS, the main dimensions of the necrosis focus were significantly smaller in the IPC group after 2 h (frontal, p=0.001; vertical, p=0.037; lesion volume, p=0.001; and lesion volume, p=0.007). Also, after 24 h, the dimensions of the lesion in the IPC group were also smaller for PTT (frontal, p<0.001; vertical, p=0.021; lesion volume, p=0.001), but not the VIM nucleus. Thus, RIPC allowed reducing the size of the PTT lesion while maintaining the clinical effect, thereby demonstrating a protective effect for the tracts adjacent to the thermal ablation zone when PTT was exposed to MRgFUS. These findings can be explained by the fact that both gray and white matter, as well as the blood-brain barrier (BBB) in them, have significant differences in anatomical structure and in the features of functioning. The BBB is not a uniform structure in the brain: it exhibits regional variability, which may influence its susceptibility to damaging factors and modify responses to treatment. The presence of specific adhesion molecules and variations in the expression of genes associated with BBB function may differ significantly between gray and white matter [12].

The following structural and functional differences can be distinguished between gray and white matter, and the BBB of gray and white matter in the brain:

- Gray matter has a higher capillary density;
- Cerebral endothelial cells in the white matter express high levels of tight junction proteins such as occludin and claudin-5 contributing to the formation of a less permeable BBB in white matter, compared with gray matter [12, 13];
- Expression of glial fibrillary acidic protein (GFAP), a marker of astrocyte function, is significantly higher in white matter, demonstrating greater involvement of astrocytes in maintaining BBB integrity in white matter [13];
- White matter BBB is more prone to rapid formation of vasogenic edema during ischemic injury [14, 15];
- White matter is more likely to develop immune-mediated inflammatory responses with subsequent (somewhat delayed) destruction of myelin [15];
- In gray matter, BBB integrity may be restored more quickly due to a higher density of glial cells, while restoration in white matter may be slower and more difficult due to significant involvement of oligodendrocytes and the need for axonal remyelination;
- IPC-mediated neuroprotection in the white matter of the brain is carried out mainly due to changes in the expression of key receptors of the immune response in microglia: toll-like receptor 4 (TLR4) and type I interferon receptor (IFNAR1), which changes the course of immune-mediated inflammation, reduces damage to oligodendrocytes and improves myelination of axons [16,17].

It can also be assumed that RIPC is potentially a promising method for protecting the brain not only from ischemic, but also from thermal exposure such FUS, radiofrequency ablation (RFA), and (possibly) from traumatic/radiation damage, which has already been confirmed in a number of studies [18].

At present, the hypothesis of a possible neuroprotective effect of IPC in cerebral ischemia and reperfusion injury of the brain is supported by clinical evidence. Preclinical studies of RIPC have demonstrated that the intervention provides both early- and late-phase neuroprotection in cerebral ischemia. The neuroprotective effects of RIPC in animal experiments have been studied in both focal and global cerebral ischemia-reperfusion injury [19].

Table 4. Intragroup comparison of parameters 2 and 24 h after MRgFUS in the IPC and sIPC groups based on the Wilcoxon test for dependent samples

Parameter	*Z statistic and p-value according to the Wilcoxon test*	
	IPC group (n=42)	sIPC group (n=39)
Frontal dimension of necrosis focus (VIM nucleus), mm	Z=-0.1156; p<0.001***	Z=-0.0784; p=0.035*
Sagittal dimension of necrosis focus (VIM nucleus), mm	Z=-0.092; p=0.031*	Z=-0.1037; p=0.004**
Vertical dimension of necrosis focus (VIM nucleus), mm	Z=-0.0917; p=0.003**	Z=-0.1098; p=0.015*
Volume of necrosis focus (VIM nucleus), mm^3	Z=-5.4031; p<0.001***	Z=-5.2641; p=0.004**
Edema size (VIM nucleus), mm	Z=-0.0779; p<0.001***	Z=-0.0971; p=0.001**
Volume of necrosis focus + VIM edema, mm^3	Z=-71.461; p<0.001***	Z=-77.733; p<0.001***
Edema volume (VIM nucleus), mm^3	Z=-66.058; p<0.001***	Z=-72.469; p<0.001***
Frontal dimension of necrosis focus (PTT), mm	Z=-0.0554; p=0.007**	Z=-0.01; p=0.01*
Sagittal dimension of necrosis focus (PTT), mm	Z=-0.0327; p=0.141	Z=-0.0659; p=0.04*
Vertical dimension of necrosis focus (PTT), mm	Z=-0.0391; p=0.1	Z=-0.0836; p=0.024*
Volume of PTT necrosis focus, mm^3	Z=-1.5111; p=0.003**	Z=-4.5501; p=0.001**
Edema size (PTT), mm	Z=-0.037; p=0.03*	Z=-0.093; p=0.002**
Volume of necrosis focus + edema (PTT), mm^3	Z=-26.915; p=0.003**	Z=-73.468; p<0.001***
Edema volume (PTT), mm^3	Z=-25.404; p=0.006**	Z=-68.918; p<0.001***

*, **, *** differences between the groups are significant at p<0.05, p<0.01 and p<0.001, respectively; MRgFUS, magnetic resonance imaging-guided focused ultrasound; IPC, ischemic preconditioning; sIPC, sham ischemic preconditioning; VIM, ventralis intermedius; PTT, pallidothalamic tract.

Neuroprotective effects of RIPC have been demonstrated in a single-center randomized controlled trial in patients with severe traumatic brain injury [20]. In the IPC group, compared with the control group, there was a significant reduction in the duration of a hospital stay and enhanced functional outcomes. Additionally, the use of RIPC therapy can reduce the concentrations of neuron-specific enolase and S100β, which suggests less pronounced neurovascular harm. The differences were statistically significant. In a randomized study in an experimental animal model of ischemic stroke, IPC administered 18 h before stroke induction (IPC group 18 h before stroke induction, IPC group 4 h after stroke induction, IPC group 5 days after stroke induction) statistically significantly reduced the size of the brain infarction focus (by 41%) and accelerated functional recovery [21]. Administration of RIPC several days after stroke induction had no effect on the size of the ischemic zone or the completeness of clinical recovery.

Neuroprotective effects of RIPC are implemented by activating a number of signaling pathways with protective function. Specifically, RIPC activates hypoxia-inducible factor (HIF-1), which regulates the expression of vascular endothelial growth factor (VEGF) and erythropoietin (EPO). This provides for neuroprotection and promotes angiogenesis, thereby improving blood supply and maintaining the functional state of the brain [22]. Another important mechanism is maintaining intracellular Ca^{2+} homeostasis via RIPC. Studies demonstrated that RIPC increases the expression of Na^{+}/Ca^{2+} exchanger 1 (NCX1), thus reducing cellular Ca^{2+} levels and the negative effects associated with its excessive accumulation [23]. RIPC inhibition of an oxidative stress represents another major advantage. Short-term ischemia episodes induced by RIPC may decrease excessive levels of reactive oxygen species (ROS) and increase levels of antioxidant enzymes such as catalase (CAT), glutathione peroxidase (GPx) and thioredoxin 2, providing additional protection to neurons in the injured area [24]. The study by Xiangnan Du et al. (2020) demonstrated that RIPC reduced the levels of IL-1β, IL-6 and IFN-γ 48 h after stroke in rats [25]. IPC-induced Thorase expression provides neuroprotection against receptor-mediated glutamate excitotoxicity by N-Methyl-D-aspartate (NMDA) [26].

Conclusion

The data obtained in our research suggest that IPC exerts a neuroprotective effect on PTT, most likely due to the modulation of the BBB at the time of formation of the necrotic area under the FUS exposure, as well as its role in reducing the severity of vasogenic edema in the white matter post-procedure.

These findings warrant further investigation into the neuroprotective mechanisms of IPC, including studies with larger patient cohorts and potential incorporation of biological markers.

Limitations

The following limitations can be identified in our study. These include the use of indirect methods for assessing the effect of IPC on the state of the BBB during FUS therapy (size dynamics of periprocedural edema around the necrotic area over time), difficulties in studying neuroprotection biomarkers, and a small sample size.

Conflict of interest

The authors stated no conflicts of interest.

Funding

This study was supported by the Russian Science Foundation grant # 24-45-00071 (https://rscf.ru/project/24-45-00071) and the National Natural Science Foundation of China (No. 82361138563).

Ethical approval

The study was conducted in accordance with the World Medical Association Declaration of Helsinki (1964) and its later amendments and approved by the Ethics Committee of Bashkir State Medical University (protocol #10 of October 13, 2023). All patients provided voluntary informed consent to receive treatment and participate in the study.

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