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Cerebral Angiogenesis and Neurogenesis in The Treatment of Ischemic Stroke in Elderly and Geriatric Patients

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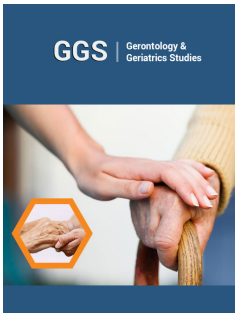

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Abstract

Aim: The research is devoted to the clinical application of transcatheter intracerebral Laser Photo Bio Modulation Therapy (PBMT) for angiogenesis stimulation, cerebral collateral blood supply restoration, neurogenesis stimulation, cerebral tissues regeneration in ischemic stroke treatment.

Methods: 953 patients aged 30-80 (average age 74.6) with ischemic stroke were examined. There were 696 men (73.03%) 257 women (26.97%).

Test group: 610 (64.01%) patients underwent transcatheter intracerebral laser PBMT, of whom 354 (58.04%) had small focal stroke, 189 (30.98%) had medium focal stroke and 67 (10.98%) had macrofocal stroke.

Control group: 343 (35.99%) patients underwent conservative treatment, of whom 256 (74.64%) had small focal stroke, 43 (12.54%) had medium focal stroke and 44 (12.82%) had macrofocal stroke.

Results

Test group: Angiogenesis stimulation, cerebral collateral blood supply restoration, neurogenesis stimulation and cerebral regenerative processes were achieved in all 610 cases regardless of the patients' age. Good clinical result was obtained in 313 (88.42%) patients with small focal strokes, in 114 (60.32%) patients with medium focal strokes, in 14 (20.90%) patients with macrofocal strokes. Satisfactory clinical result was obtained in 36 (10.17%) patients with small focal strokes, in 48 (25.39%) patients with medium focal strokes, in 27 (40.30%) patients with macrofocal strokes.

Control group: Good clinical result was obtained in 51 (19.92%) patients with small focal strokes; patients with medium focal and macrofocal strokes showed no good result. Satisfactory clinical results were obtained in 63 patients (24.61%) with small focal strokes and in 8 patients (18.60%) with medium focal strokes. No satisfactory results were obtained in patients with macrofocal strokes.

Conclusion: Angiogenesis and neurogenesis are important directions in ischemic stroke treatment. Transcatheter intracerebral laser PBMT stimulates these processes and is an effective, pathogenetically substantiated method for ischemic stroke treatment. The method normalizes cerebral blood supply, causes tissue regeneration, which leads to the restoration of daily life, cognitive and mental functions in young as well as in elderly and geriatric patients.

Keywords: Ischemic stroke; Therapeutic targets; Transcatheter intracerebral laser photobiomodulation therapy; PBMT; Angiogenesis; Neurogenesis; Regeneration

Introduction

In recent years, ischemic stroke has become one of the most common causes of patients' severe disability and death. In the United States alone 159,050 people died from stroke in 2020 [1]. Ischemic stroke is actively spreading: 7.59 million cases were registered in all countries in 2020 [2]. The brain is the most actively blood supplied organ in the human body, it has complex angioarchitecture and microcirculation [3,4]. The large arteries carry out a transporting function and only deliver blood to the cerebral peripheral bed. It is the intracerebral capillary bed that plays the main role in cerebral blood supply, oxygenation and in ensuring neuronal metabolism [3,4]. One cubic centimeter of cerebral tissue contains about 3-4 thousand capillaries [3]. The brain is extremely sensitive to decreased blood supply

and subsequent hypoxia, which very quickly leads to ischemia, death of cerebral tissue and stroke development [3-7]. The more extensive the ischemic zone is, the more it spreads to various cerebral regions, the more severe the stroke and its consequences are [3, 5, 6]. The main cause of cerebral ischemia is atherosclerosis, which leads to stenosis, subsequent thrombosis and occlusion of extracranial, intracerebral arteries, arterioles and capillaries [4,6]. The extracranial type of atherosclerotic lesion occurs in 9.33% of cases, the mixed type in 46.19% of cases, the intracerebral type in 44.53% of cases [6]. The development of cerebral ischemia and ischemic stroke cause both destructive and restorative processes in the brain [3,6,8,9]. Under natural conditions, the organism strives to reduce the damage caused and responds to ischemia development with a complex of complicated reactions aimed at revascularization and restoration of cerebral tissue. A decrease in blood flow in intracerebral arteries and capillaries stimulates angiogenesis, which leads to the development of the collateral bed. The collateral bed delivers blood to the ischemic areas of the brain from other, unaffected arterial basins [3,4,6,8,9]. With aging, cerebral blood supply decreases, which stimulates angiogenesis, leading to the development of the collateral bed. As a result, older patients have milder ischemic strokes than younger ones, in whom collateral blood supply has not yet developed [3,4,6-8].

Simultaneously, angiogenesis and collaterals development are neuroprotectors that stimulate the processes of neurogenesis and regeneration of cerebral tissues [3-6,8-11]. Unfortunately, these natural physiological processes occur quite slowly and after an ischemic stroke, they do not lead to rapid, clinically significant recovery [6]. Many authors note the extremely important significance of stimulating cerebral angiogenesis and neurogenesis in the treatment of cerebrovascular insufficiency and ischemic stroke [2,4,6-11]. Conservative treatment methods common in modern practice do not have clear directions of affecting cerebral tissues. The effectiveness of existing drugs is quite limited [4,6,8,9]. As a result, conservative treatment is usually effective for small focal strokes with minor areas of neurosecretion and neurodegeneration [4,12]. For more extensive ischemic strokes, as well as those in elderly patients, conservative treatment becomes less effective [6,9,11-13]. A particular group in the treatment of ischemic stroke is stem cell therapy methods. However, this promising area is still under development [9,10].

Conducting interventional and reconstructive surgeries is aimed at improving the main blood supply and is usually carried out on large arterial trunks. These methods have proven themselves effective in operations on brachiocephalic arteries in younger patients [13-17]. In case of intracerebral atherosclerotic lesions, these interventions are difficult to carry out due to the small diameter and intracranial location of the vessels [6,14,15]. Systemic and local thrombolysis, transcatheter mechanical thrombectomy and thromboextraction are also aimed at restoring the main cerebral blood supply. These methods are advisable to be used only in the acute stage of ischemic stroke [18,19]. When using these methods, certain difficulties arise in determining the neuroprotective effect [20]. This situation in the treatment of cerebrovascular lesions and ischemic stroke requires the development of new, effective methods aimed at both dealing with various processes that occur during the development of hypoxia, ischemia and neurosecretion and at stimulating recovery processes. These methods should include a comprehensive impact on angiogenesis, neuroprotection and neurogenesis [4,6-9]. One of the promising areas in the treatment of cerebrovascular lesions and ischemic stroke is the use of laser energy [4,6,7,21-30]. The use of laser energy for medical purposes began almost immediately after the discovery of the laser effect, in the 1960s. In 1967, E. Mester et al. were the first to use a ruby laser with low output power to restore hair covering [31]. In 1968, N. S. Makeeva and V. V. Schur successfully used a helium-neon laser to heal superficial skin wounds [32].

Currently, this direction in laser medicine, using a laser with low output power, is called laser Photobiomodulation Therapy (PBMT) [4,7,21-24]. In the treatment of ischemic, neurodegenerative and traumatic cerebral lesions, PBMT uses a laser with low output power of the red or near-infrared spectral range (wavelength 600-1100nm). With PBMT, laser exposure has a precise direction and has a multicomponent, complex effect on cerebral tissues [22,23,24]. Laser energy acts at the molecular, cellular and tissue levels. This effect stimulates the formation of active oxygen forms, increases mitochondrial oxygen consumption, restores Adenosine Triphosphate (ATP) metabolism in mitochondria, stimulates and restores metabolic processes in neurons, stimulates angiogenesis, causes the opening of collateral vessels, improves cerebral blood flow, eliminates vascular dysfunction, increases tissue oxygenation, stimulates lymphatic drainage, improves blood flow, reduces apoptosis, stimulates neurogenesis and synaptogenesis, causes cerebral tissue regeneration and the development of intercellular connections [4,6,7,21-29]. The energy of the laser with low output of the red spectral range, when directly applied to the brain, deeply penetrates the cerebral tissue. At a wavelength of 600 to 700nm, the penetration depth is 20-40mm [33]. At a wavelength of 808nm, it is 40-50mm [34]. For various brain lesions, laser PBMT includes transcranial [7,22,23] intranasal (often in combination with transcranial) [24,25,35] intravascular (intravenous) [36] и and transcatheter intracerebral treatment methods [4,6,21,30,33]:

A. Transcranial is a non-invasive, fairly simple method. Laser energy is supplied to the scalp; special helmets with several LED emitters are often used to increase the area of exposure [7,22,23,26,27]. To reach the brain, laser energy passes through the tissues of the scalp, skull bones and meninges. These structures have a high degree of absorption and a fairly low degree of light transmission, which reduces the level of laser energy reaching the brain. As a result, a limited amount of energy reaches the cerebral tissues. In this regard, to obtain a stable clinical effect, it is necessary to conduct a sufficiently large number of sessions [22,23,29]. The treatment results do not depend on the patients' age.

B. Intranasal (sometimes transpenoidal) is also a fairly simple, minimally invasive method. Laser energy is supplied to the brain through the nasal cavities [24]. Laser energy

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passes through the mucous membranes of the nose and the thinner bones of the skull. These tissues have a lower degree of absorption and a higher degree of transmission of laser energy. With this method of supply, more energy reaches the brain. But this method also requires a sufficiently large number of sessions. For a total increase in laser energy penetrating into the brain tissue and enhancing the therapeutic effect, the intranasal method is often combined with the transcranial method [25, 35]. The treatment results do not depend on the patients' age.

C. Intravascular (intravenous) is a fairly simple, minimally invasive method. During its implementation, through a peripheral intravenous catheter is inserted a fiber optic light-guiding instrument, through which the blood and vascular wall are exposed to the laser. There is no direct effect of laser energy on brain tissue. According to the authors, the method provides a pronounced clinical effect in patients who have suffered their first limited ischemic stroke. To obtain a stable positive clinical effect, at least 10 sessions are necessary [36]. The treatment results do not depend on the patients' age.

D. Transcatheter intracerebral is also a minimally invasive, interventional, but more complex method. The intervention is carried out in catheterization laboratories. Under fluoroscopic control, a peripheral artery is catheterized. Using interventional technology, a flexible small-diameter laser fiber-optic light-guiding instrument connected to the laser unit is passed through the peripheral and then carotid arteries to the affected intracerebral arterial branch. Laser exposure is performed through this fiber-optic instrument. Due to the greater amount of laser energy, one intervention is sufficient to obtain a pronounced positive clinical effect [4,6,30,33,37]. The treatment results do not depend on the patients' age.

The present study is devoted to the clinical application of transcatheter intracerebral laser Photobiomodulation Therapy (PBMT) for stimulation of angiogenesis, restoration of cerebral collateral arterial and capillary blood supply, stimulation of neurogenesis and regeneration of cerebral tissues in the treatment of ischemic stroke in young patients and in elderly and geriatric patients.

Materials and Methods

Diagnostics and intracerebral transcatheter laser interventions, as well as conservative treatment in this research, were performed with the approval of the ethics committee (Protocol No. 2 of 01-04-1996, Protocol No. 4 of 01-12-2002, Protocol No. 12 of 03-26-2015, Protocol No. 12 of 04-15-2021) and the consent of patients and their relatives.

Patient selection criteria:

a) consent of patients and their relatives to the necessary examination and treatment.

b) patients' somatic condition allowing the necessary examination and treatment.

c) patients' cerebral ischemic stroke history in the period from 6 months to 6 years.

d) cerebral structural changes, signs of daily life deterioration, cognitive impairment and dementia in patients.

Patient examinations

A. Cerebral structural changes were determined using CT and MRI according to generally accepted schemes.

B. Daily life activities were assessed using the Bartels Functional Evaluation (IB) Index [38].

C. Cognitive functions were assessed using the Mini-Mental State Examination (MMSE) [39].

D. The severity of dementia was assessed using the Clinical Dementia Rating scale (CDR) [40].

E. Laboratory examination: coagulological, biochemical and general clinical tests.

F. Cerebral blood flow was assessed using Scintigraphy (SG) with TC 99M Pertechnetate 555.

G. Impaired pulse blood filling in the cerebral hemispheres was assessed using Rheoencephalography (REG).

H. The condition of the cerebral vascular and microcirculatory bed was assessed using cerebral Multi-Gated Angiography (MUGA) in the direct and lateral projections [6,30]. Capillary blood flow was determined using the computer program "Angio Vision" [4,33,41-44]. In some cases, Multiperil Computed Tomography Angiography (MSCTA) or Magnetic Resonance Angiography (MRA) were carried out in the remote period.

Analysis of Patients

953 patients aged 30-80 (mean age 74.6) who had had an ischemic stroke in the period from 6 months to 6 years were examined: 696 (73.03%) were men and 257 (26.97%) were women.

Test group-

610 (64.01%) patients underwent transcatheter intracerebral laser PBMT of whom:

a) 354 (58.04%) patients with small focal stroke.

b) 189 (30.98%) patients with medium focal stroke.

c) 67 (10.98%) patients with macrofocal stroke.

Control group-

343 (35.99%) patients underwent conservative treatment, of whom:

a) 256 (74.64%) patients with small focal stroke.

b) 43 (12.54%) patients with medium focal stroke.

c) 44 (12.82%) patients with macrofocal stroke.

All patients in the test and control groups had similar age, somatic conditions, stroke severity, time after stroke and post-ischemic cyst sizes.

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The results of the initial examination of patients in the study and control groups are presented in Table 1.

Table 1: Patient examination data

Characteristic of Identified Changes	Test group (N-610)	Control Group (N-343)
Cerebral CT and MRI		
Multiple deposits of calcium salts in intracerebral vessels	504 (82.62%)	285 (83.09%)
General involutive brain changes	512 (83.97%)	288 (83.97%)
Expansion of the subarachnoid space	501 (82.13%)	278 (81.05%)
Enlargement of the Sylvian fissures	514 (84.26%)	290 (84.55%)
Symptoms of non-occlusive hydrocephalus	378 (61.97%)	216 (62.97%)
Small focal strokes	354 (58.04%)	256 (74.64%)
Medium focal strokes	189 (30.98%)	43 (12.54%)
Macrofocal strokes	67 (10.98%)	44 (12.82%)
Daily Activity		
Decrease in Barthel Index (BI) below 95 points	332 (54.43%)	181 (52.77%)
Decrease in Barthel Index (BI) below 80 points	212 (34.75%)	112 (32.65%)
Decrease in Barthel Index (BI) below 60 points	66 (10.82%)	50 (14.58%)
Cognitive Disorders		
Decrease to 20-25 MMSE points	335 (54.92%)	188 (54.81%)
Decrease to 12-19 MMSE points	239 (39.18%)	134 (39.07%)
Decrease to 7-11 MMSE points	36 (5.90%)	21(6.12%)
Clinical Dementia Determination		
No symptoms of dementia	54 (8.85%)	42 (12.24%)
CDR-1	336 (55.08%)	148 (43.15%)
CDR-2	181 (29.68%)	115 (33.53%)
CDR-3	39 (6.39%)	38 (11.08%)
Cerebral scintigraphy (SG)		
Decreased blood flow in cerebral hemispheres	610 (100%)	343 (100%)
Cerebral Rheoencephalography (REG)		
Decreased volumetric pulse blood supply in the carotid system	610 (100%)	343 (100%)
Cerebral Multi-Gated Angiography (MUGA)		
Stenotic lesions in the distal pools of intracerebral branches	610 (100%)	343 (100%)
Occlusive lesions in the distal pools of intracerebral branches	610 (100%)	343 (100%)
Two-sided atherosclerotic lesions	585 (95.90%)	329 (95.92%)

Test Group

Patients in the test group underwent Transcatheter Intracerebral Laser Photobiomodulation Therapy (PBMT). Under local anesthesia, using the Selinger method, the common femoral artery is catheterized. A guiding microcatheter is coaxially inserted and led across the vascular bed through the carotid artery to the affected intracerebral branches. A flexible fiber-optic light-guiding instrument, with a diameter of 25 to 100 micrometers, connected to a helium-neon laser (wavelength 632.8nm), is inserted through this catheter. Thanks to this light-guided instrument, intracerebral laser exposure is made possible (the laser exposure characteristics: fiber output power of 24-45mW, beam spot diameter in the vessel of 1-2mm, average dose during treatment of 29-106J, treatment session duration of 1200-2400 seconds) [30,37,42-44]. This method allows for targeted, direct exposure to the endothelium, vascular wall, blood and surrounding cerebral tissues. The insignificant thickness of the fiber-optic instruments allows for working with small-diameter intracerebral arterial branches, which significantly distinguishes this method from other interventional treatment methods. Since atherosclerosis is a systemic disease, it affects intracerebral arteries, arterioles and capillaries of both hemispheres. The severity of the lesion may vary; in one hemisphere, atherosclerotic changes may be more pronounced than in the other. But in the hemisphere with less pronounced atherosclerosis, vascular changes that reduce intracerebral blood flow still exist and they contribute to hypoxia and ischemia [3-5,8,12,13]. For this reason, to improve the blood supply to the entire brain, transcatheter intracerebral PBMT was performed in all cases on both sides, in both the right and left hemispheres [30,41-44]. At the end of the transcatheter intracerebral intervention, a repeated cerebral MUGA is performed. The results of MUGA are used to determine the severity of intracerebral angiogenesis, the degree of collateral, capillary revascularization. After transcatheter, intracerebral laser

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PBMT, the patients underwent complex antiplatelet, anticoagulant, antioxidant, vasodilator and nootropic therapy. In accordance with the parameters of the blood coagulation system, the patients took Aspirin, Heparin and indirect anticoagulants. Intravenously, they took 10-15 infusions of Pentoxifylline 100mg, Complamin 150mg, Inosin 200mg, Nootropil (Piracetam) 1200mg (or Gliatilin 1000mg) followed by pills. In subsequent periods of treatment, courses of infusions and pills were repeated 2 times a year for 1-2 months.

Control Group

The patients of the control group underwent conservative treatment using similar regimens and doses of drugs used in the postoperative period by patients of the test group. In accordance with the parameters of the blood coagulation system, the patients took Aspirin, Heparin, indirect anticoagulants, 10-15 infusions of Pentoxifylline 100mg, Complamin 150mg, Inosin 200mg, Nootropil (Piracetam) 1200mg (or Gliatilin 1000mg) followed by pills. In the subsequent period, the patients also underwent repeated courses of infusions and pills 2 times a year for 1-2 months.

Evaluation of Results After the Treatment

The results obtained after the treatment were considered as:

a) Good clinical result-almost complete recovery of motor, cognitive and mental functions (IB 95-100, MMSE 27-30, no dementia).

b) Satisfactory clinical result-incomplete recovery of motor, cognitive and mental functions (IB 85-90, MMSE 25-27, the level of dementia has decreased).

c) Relatively satisfactory clinical result-partial recovery of motor, cognitive and mental functions (IB below 80, MMSE below 25, the level of dementia has decreased but it remains).

d) Relatively positive clinical result-no negative dynamics with minor recovery of motor, cognitive and mental functions.

Results

Test group

Immediate results: According to cerebral angiography (MUGA), after transcatheter intracerebral laser PBMT, an immediate positive result, manifested by pronounced angiogenesis, collateral and capillary revascularization, was obtained in 608 (99.67%) patients (Figures 1B, 1C, 2B, 2C, 3B, 3C). In 2 (0.33%) patients, angiogenesis was manifested to a lesser extent. Complications associated with these interventions were not observed.

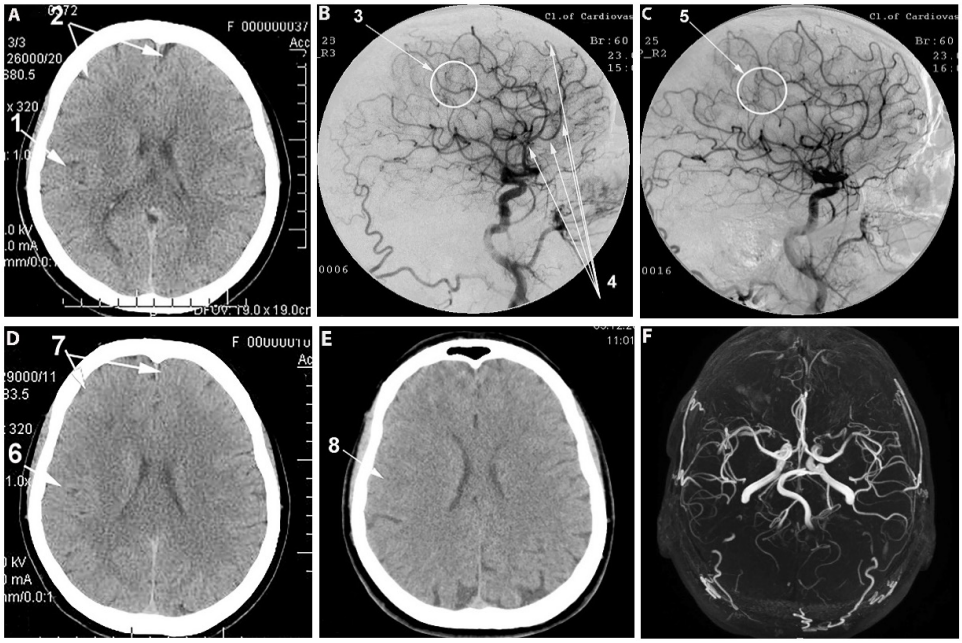

Figure 1: Patient H., female, 60 years old. Atherosclerosis of cerebral vessels, chronic cerebrovascular insufficiency ischemic stroke in the basin of the middle cerebral artery to the right. Before and after transcatheter intracerebral PBMT.

A. CT of the brain, before the intervention: 1. moderate heterogeneous postischemic cyst in the right middle cerebral artery region. 2. moderate expansion of the subarachnoid space.

B. Right internal carotid artery angiogram, arterial phase, before the intracerebral laser PBMT: 3. occlusion of distal branches of the right middle cerebral artery; 4. multiple stenosis of intracranial branches.

C. Right internal carotid artery angiogram, arterial phase, after the intracerebral laser PBMT: 5. Stimulation of angiogenesis, collateral arterial and capillary revascularization of the right hemisphere.

D. CT of the brain, 12 months after the intracerebral laser PBMT: 6. reduction in the size of the post-ischemic cyst with signs of cerebral tissue structure recovery; 7. subarachnoid space restoration.

E. CT of the brain, 6 years after the intracerebral laser PBMT: 8. the structure of the right hemisphere cerebral tissue is restored, no signs of residual effects of the post-ischemic cyst.

F. MRA of the brain. 10 years after the intracerebral laser PBMT: the patency and lumen of the distal branches of the right internal carotid artery are completely preserved, there is further progression of collateral revascularization.

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Early period (1-6 months) after transcatheter intracerebral laser PBMT: According to the results of SG and REG, improvement of cerebral blood flow and volumetric pulse blood filling in the hemispheres was observed in all 610 (100%) patients. According to the results of CT and MRI, a tendency to a decrease in general involutional changes in the brain, as well as narrowing of the subarachnoid space and a decrease in the volume of post-stroke cysts, were observed in all 610 (100%) patients (Figures 1A, 1D, 2A, 2D). According to the results of testing (IB, MMSE and CDR), pronounced positive clinical dynamics was observed in all 610 (100%) patients.

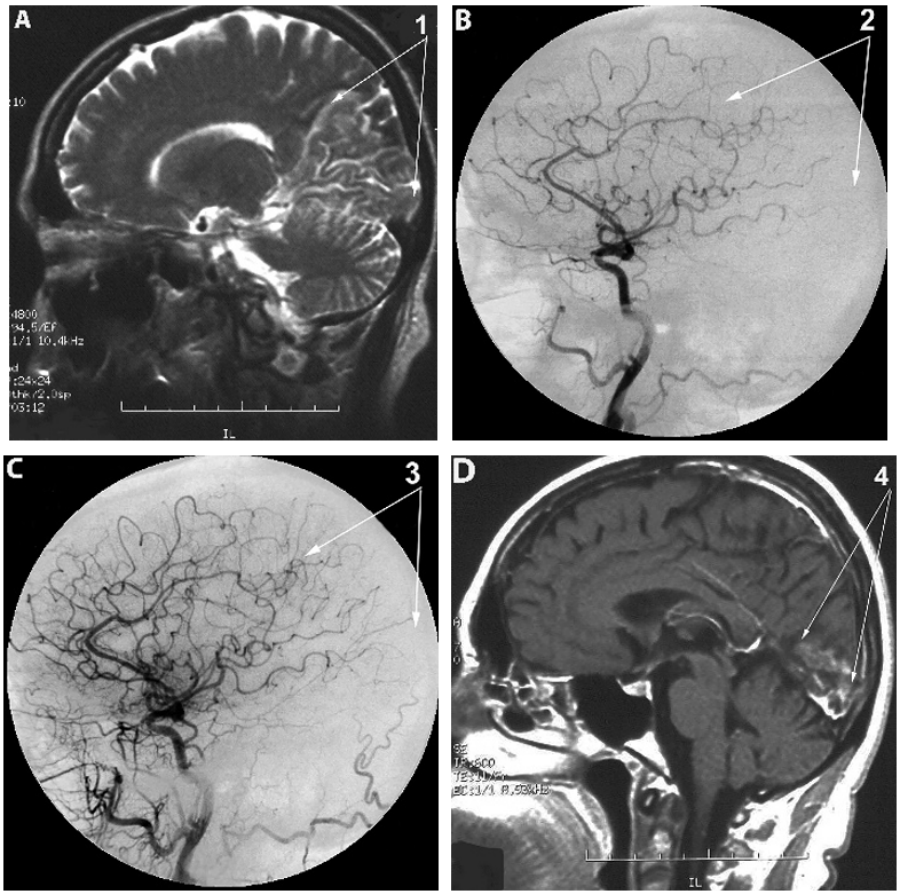

Figure 2: Patient A., female, 58 years old (BI-50, CDR-2). Atherosclerosis of cerebral vessels, chronic cerebrovascular insufficiency, extensive ischemic stroke in the occipital parietal region of the right hemisphere. Before and after transcatheter intracerebral PBMT.

A. MRI of the brain, before the intervention: 1. extensive postischemic cyst in the right occipital parietal region of the right hemisphere.

B. Right internal carotid artery angiogram, arterial phase, before the intracerebral laser PBMT: 2. multiple occlusions of the distal branches of the right medial cerebral artery.

C. Right internal carotid artery angiogram, arterial phase, after the intracerebral laser PBMT: 3. stimulation of angiogenesis, marked collateral arterial and capillary revascularization of the right hemisphere.

D. MRI of the brain, 10 months after the intracerebral laser PBMT: 4. significant reduction in the size of the post-ischemic cyst with signs of cerebral tissue structure recovery.

Remote period (1-10 years) after transcatheter intracerebral laser PBMT: According to the results of repeated SG and REG, 1-2 years after PBMT, the improvement in cerebral blood flow and volumetric pulse filling obtained in the early period was observed in all 610 (100%) patients and was maintained throughout the entire observation period. According to the results of repeated CT and MRI, 1-2 years after PBMT

a) Of 512 patients (Table 1) a decrease in general involutional changes in the cerebral cortex was observed in 491 (95.90%) cases (Figures 1A,1D,2A,2D).

b) Of 501 patients (Table 1), narrowing of the subarachnoid space was observed in 479 (95.61%) cases.

c) Of 514 patients (Table 1) narrowing of the Sylvian fissures was observed in 493 (95.91%) cases.

d) Of 378 patients (Table 1) a decrease in the symptoms of non-occlusive hydrocephalus was observed in 242 (64.02%) cases.

e) A decrease in the volume of post-ischemic cysts after stroke was observed in all 610 patients. Of these, a decrease

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of 5-15% was noted in 71 (11.64%) cases, 15-25% in 206 (33.77%) cases, more than 25% in 333 (54.59%) cases (Figures 1A, 1D, 1E, 2A, 2D, 3A, 3D).

In the subsequent period (over 2 years), positive dynamics were maintained throughout the entire observation period in all 610 (100%) patients (Figures 1A, 1E, 3A, 3D). According to the results of repeated testing (IB, MMSE and CDR) in the subsequent period of over 2 years, pronounced positive clinical dynamics was observed in all 610 (100%) patients. According to the results of repeated MUGA, MSCTA, MRA in the period of 2 - 10 years after the performed PBMT, 232 (38.03%) patients were examined, with angiogenesis, collateral and capillary revascularization persisting in 229 (98.71%) cases (Figures 1C, 1F).

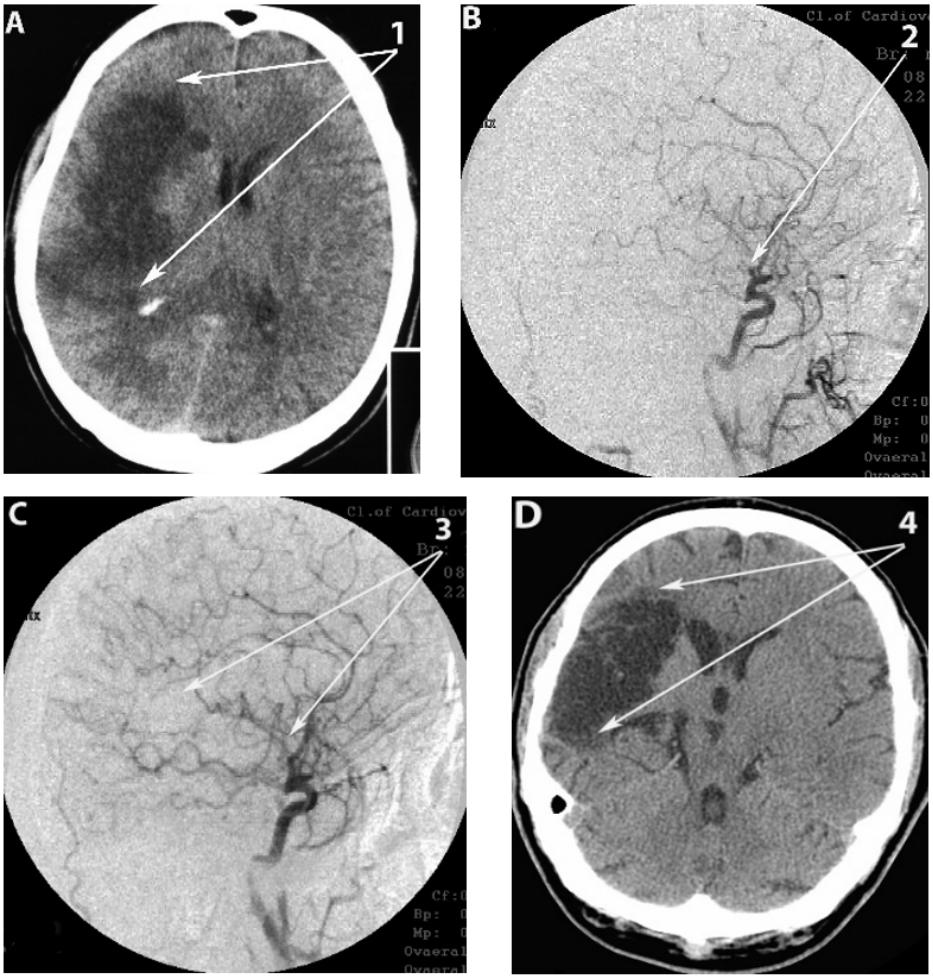

Figure 3: Patient J, male, 41 years old, (BI-40 CDR-3). Atherosclerosis of cerebral vessels, macrofocal ischemic stroke of the right hemisphere before and after transcatheter intracerebral laser PBMT.

A. CT of the brain, before the intracerebral PBMT: 1. huge postischemic cyst in the right middle cerebral artery region.

B. Right internal carotid artery angiogram, arterial phase, before the intracerebral laser PBMT: 2. Occlusion of the right middle cerebral artery.

C. Right internal carotid artery angiogram, arterial phase, after the intracerebral PBMT: 3. Pronounced collateral and capillary revascularization of the right hemisphere with good peripheral blood flow.

D. CT of the brain, 10 years after intracerebral PBMT: 4. Preservation and progression of pronounced collateral revascularization of the right hemisphere with good peripheral blood flow (BI-100).

Control Group

Immediate results

After the course of conservative treatment, negative dynamics was not observed in any of 343 (100%) patients. Stabilization of the condition was observed in 78 (22.74%) cases. Positive dynamics, manifested by a moderate decrease in motor and mental disorders, was observed in 265 (77.26%) cases.

Early period (1-6 months) after the conservative treatment

According to the results of repeated SG and REG, unstable improvement of cerebral blood flow and volumetric pulse blood filling was observed:

a) in 204 (79.69%) cases out of 256 patients (Table 1) with small focal strokes.

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b) in 14 (32.56%) cases out of 43 patients (Table 1) with medium focal strokes.

c) in 8 (18.18%) cases out of 44 patients (Table 1) with macrofocal strokes.

According to the results of CT and MRI, there were no signs of a significant decrease in involutional cerebral changes, narrowing of the subarachnoid space, Sylvian fissures, a decrease in the phenomena of non-occlusive hydrocephalus or a decrease in the volume of post-stroke cysts in any of the 343 (100%) patients.

According to the results of repeated IB, MMSE and CDR testing, partial improvement of motor and mental functions was observed:

a) in 238 (92.97%) cases out of 256 patients (Table 1) with small focal strokes.

b) in 11 (25.58%) cases out of 43 patients (Table 1) with medium focal strokes.

c) in 7 (15.91%) cases out of 44 patients (Table 1) with macro focal strokes.

The remaining 87 (25.36%) patients showed stabilization of their condition.

Remote period (1-10 years) after the conservative treatment

According to the results of SG and REG performed 1-2 years after conservative treatment

a) of 204 patients with small focal strokes who showed positive dynamics in the early period, the indicators decreased in 113 (55.39%) cases.

b) of 14 patients with medium focal strokes who showed positive dynamics in the early period, the indicators decreased in 7 (50.00%) cases.

c) of 8 patients with macrofocal strokes who showed positive dynamics in the early period, the indicators decreased in 3 (37.50%) cases.

d) The remaining 117 (34.11%) patients showed instability of indicators.

In the subsequent period (over 2 years), all 343 patients showed a tendency towards a decrease in indicators.

According to the results of CT and MRI performed 1-2 years after the conservative treatment, significant signs of a decrease of involutional changes in brain tissue, narrowing of the subarachnoid space, narrowing of the Sylvian fissures, a decrease of non-occlusive hydrocephalus were not observed in any of the 343 patients. A decrease in the volume of post-ischemic cysts was not observed in any of the 343 patients. In the subsequent period (over 2 years), of all 343 patients in the control group, an increase in involutional changes, widening of the Sylvian fissures and symptoms of non-occlusive hydrocephalus were observed in 249 (72.59%) cases. According to the results of repeated IB, MMSE and CDR testing in the period of 1-2 years, the indicators of positive clinical dynamics with improvement of motor and mental functions changed.

The improvement was noted:

a) in 238 (92.97%) cases out of 256 patients (Table 1) with small focal strokes.

b) in 12 (27.91%) cases out of 43 patients (Table 1) with medium focal strokes.

c) in 7 (15.91%) cases out of 44 patients (Table 1) with macrofocal strokes.

The remaining 86 (25.07%) patients showed stabilization of their condition.

According to the results of repeated testing (IB, MMSE and CDR) in the subsequent period of over 2 years, a decrease in the indicators was observed in all 343 patients (Table 2).

Table 2: Clinical Results in the remote period (1-10 years) after the treatment.

Treatment Clinical Result	Test Group (N-610)	Control Group (N-343)	p (chi-square)
Patients with small focal strokes			
Total number of patients	354	256	
Good clinical result	313 (88.42%)	51 (19.92%)	$p < 0.005$
Satisfactory clinical result	36 (10.17%)	63 (24.61%)	$p < 0.005$
Relatively satisfactory clinical result	5 (1.41%)	107 (41.80%)	$p < 0.005$
Relatively positive clinical result	0	35 (13.67%)	$p < 0.005$
Patients with medium focal strokes			
Total number of patients	189	43	
Good clinical result	114 (60.32%)	0	$p < 0.005$
Satisfactory clinical result	48 (25.39%)	8 (18.60%)	$p < 0.005$
Relatively satisfactory clinical result	27 (14.29%)	11 (25.58%)	$p < 0.005$
Relatively positive clinical result	0	24 (55.82%)	$p < 0.005$

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Patients with macrofocal strokes			
Total number of patients	67	44	
Good clinical result	14 (20.90%)	0	p < 0.005
Satisfactory clinical result	27 (40.30%)	0	p < 0.005
Relatively satisfactory clinical result	26 (38.80%)	8 (18.18%)	p < 0.005
Relatively positive clinical result	0	36 (81.82%)	p < 0.005

Due to well-known criteria and information on statistical data processing in medical research and practice, the differences between groups of patients are determined according to the analysis of the relevant 2 x 2 contingency tables using the Pearson chi-square test. The corresponding p-values are listed in the last column of the table. p = 0.05.

Discussion

Regardless of the patient's age, treatment of ischemic stroke and its consequences should be physiologically justified, multicomponent, complex, directed at stimulation of angiogenesis and neurogenesis for revascularization and regeneration of cerebral tissues [4,6,8,9,37]. Common methods of conservative treatment of ischemic stroke consequences often do not have clear, specific directions of affecting cerebral tissues and at the same time, they are limited by the insufficient effectiveness of existing drugs [4,9]. Modern drugs used in clinical practice can improve blood supply, but do not stimulate angiogenesis and do not allow achieving pronounced, persistent cerebral revascularization. Modern drugs can affect metabolic and neuroprotective processes, but do not cause neurogenesis and regeneration of cerebral tissue. This often leads to the fact that against the background of the therapy, it is not always possible to achieve a pronounced therapeutic effect. In patients of the control group, repeated SG and REG performed at different stages of conservative treatment showed no pronounced, persistent improvement in cerebral blood supply and pulse blood filling. Unstable improvement in the indicators was observed mainly in patients with small-focal and medium focal strokes in the early period of treatment (1-6 months). In the late period (1-10 years), the obtained positive dynamics gradually decreased. Repeated CT and MRI carried out at different stages of treatment showed no signs of a decrease in involutional changes or the development of regenerative processes in cerebral tissue. Repeated IB, MMSE and CDR testing at different stages of treatment showed positive dynamics in daily life, cognitive functions and the level of dementia in a limited number of patients with small-focal and medium-focal strokes. As a result, in the control group, good and satisfactory clinical results were observed only in 114 (44.53%) patients with small-focal and in 8 (18.60%) patients with medium focal ischemic stroke. The obtained results are consistent with the data of other authors [2,9].

Brain tissue is an optically active medium [33]. In ischemic, neurodegenerative and traumatic cerebral lesions, lasers with low output power of the red or near-infrared spectral range have a complex mechanism of affecting cerebral tissues. As shown by numerous studies conducted in various countries, laser energy has a targeted effect on brain tissue. The effect occurs at the molecular, cellular and tissue levels, causing physiological angiogenesis and neurogenesis. As a result, regardless of patients' age, vascular dysfunction is eliminated, collateral arterial and capillary revascularization develops, cerebral blood flow improves, tissue oxygenation increases, venous outflow is normalized, apoptosis decreases and regenerative processes in cerebral tissue develop [4,6,7,18,21-23,26,29,37]. Transcatheter intracerebral laser PBMT allows to accurately, listlessly deliver the required amount of laser energy to the site of cerebral damage, directly affecting the endothelium, vascular wall and surrounding cerebral tissues. In the test group of patients, repeated cerebral angiographic studies (MUGA, MSCTA and MRA), performed at different times after transcatheter intracerebral laser PBMT, showed persistent, pronounced collateral cerebral revascularization in 229 (98.71%) cases out of 232 re-examined patients.

Repeated cerebral SG, REG in the early (1-6 months) and late periods (1-10 years) showed that stimulation of angiogenesis with laser energy leads to a long-term, stable improvement in cerebral blood flow and volumetric pulse blood filling in all 610 (100%) cases. Repeated cerebral CT and MRI in the early period (1-6 months) already showed a decrease in involutional changes and a tendency to restoration of cerebral tissues in all 610 (100%) cases. In the late period (1-10 years) after transcatheter intracerebral laser PBMT, repeated cerebral CT and MRI clearly showed a decrease in involutional changes in the cerebral cortex, narrowing of the subarachnoid space, narrowing of the Sylvian fissures and a decrease in the phenomena of non-occlusive hydrocephalus and also a decrease in the size of the post-ischemic cyst with the restoration of normal cerebral tissue in all 610 (100%) cases. This dynamic indicates the development of cerebral regenerative processes. As a result, regardless of age, the patients of the test group showed restoration of their daily life (IB), cognitive functions (MMSE), as well as a decrease in dementia symptoms (CDR). In the remote period, regardless of age, the patients of the test group showed positive dynamics in 610 (100%) cases and good and satisfactory clinical results were obtained in 552 (90.49%) cases in patients with small focal strokes, medium focal strokes and macrofocal strokes (Table 2). showed positive dynamics in 610 (100%) cases and good and satisfactory clinical results were obtained in 552 (90.49%) cases in patients with small focal strokes, medium focal strokes and macrofocal strokes (Table 2). The obtained results confirm the data of other authors who showed positive results in the implementation of various PBMT methods for the treatment of the consequences of ischemic stroke [7,22-29].

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Conclusion

Angiogenesis and neurogenesis are an important direction in the treatment of ischemic stroke. By stimulating angiogenesis and neurogenesis, transcatheter intracerebral laser PBMT is a physiologically and pathogenetically substantiated, effective method for treating ischemic stroke and its consequences, regardless of the patients' age. By stimulating angiogenesis, laser energy opens collateral arterial and capillary beds and, thereby, causes revascularization of the ischemic hemisphere. Simultaneous intracerebral PBMT in the opposite hemisphere leads to normalization of blood supply to the entire brain.

Deeply affecting cerebral tissues, transcatheter intracerebral laser PBMT, regardless of the patients' age, stimulates neurogenesis. Laser energy improves cellular and tissue metabolism, restores ATP metabolism in neuronal mitochondria and produces active oxygen forms. Simultaneously, synaptogenesis is stimulated, and intercellular connections are restored. This multicomponent effect leads to the regeneration of cerebral tissues. Complex and low-traumatic effect of transcatheter intracerebral laser PBMT in ischemic strokes of varying severity, regardless of the patients' age, allows to achieve rapid and stable rehabilitation of patients. As a result, patients have their daily life and cognitive functions restored and symptoms of dementia reduced, which allows them to return to an independent, active, full life. The positive clinical effect obtained after transcatheter intracerebral laser PBMT is observed for a long time, both in younger patients and in elderly and geriatric patients, which significantly distinguishes this method from other methods of treatment. Conservative treatment methods generally provide a positive clinical result in younger patients with mild forms of cerebral ischemic damage. The positive result is usually observed after small focal or medium focal strokes.

Declaration of Conflicting Interests

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