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RESEARCH ARTICLE

Study of the Impact of Transcatheter Intracerebral Laser Photobiomodulation Therapy Treatment on Patients with Alzheimer's Disease and Binswanger's Disease

Ivan V. Maksimovich

Clinic of Cardiovascular Diseases named after Most Holy John Tobolsky, Building 2, Block 15, 6th Lazenki Str., 119619 Moscow, Russia

*carvasc@yandex.ru

Abstract

Background: Alzheimer's disease (AD) and Binswanger's disease (BD) are among the most common neurodegenerative disorders associated with cognitive impairment and dementia. Using energy of lasers with low output power of the red or near-infrared spectrum region called Photobiomodulation Therapy (PBMT), is an achievement in the development of methods for the treatment of these diseases.

Aims: The present study investigates the impact of Transcatheter Intracerebral Laser Photobiomodulation Therapy (PBMT) on the reduction of cognitive, mental impairment and dementia in patients with various Alzheimer's Disease and Binswanger's Disease stages.

Methods: For the research, we selected 62 patients suffering from dementia, aged 34-81 (mean age 72.75), 25 men (40.32%), 37 women (59.68%).

Test Group 1 - 48 patients previously diagnosed with Alzheimer's Disease. According to dementia severity, patients were subdivided: preclinical stage (dementia level TDR-0) - 4, mild stage (dementia level TDR-1) - 16, moderately severe stage (dementia level TDR-2) - 21, severe stage (dementia level TDR-3) - 7.

Test Group 2 - 14 patients with previously diagnosed Binswanger's Disease. According to dementia severity, the patients were subdivided: mild stage (dementia level CDR-1) - 9, moderately severe stage (dementia level CDR-2) - 5.

All patients underwent Transcatheter Intracerebral Laser Photobiomodulation Therapy (PBMT).

Results:

Test Group 1. Thanks to angiogenesis and neurogenesis stimulation using Transcatheter Intracerebral Laser Photobiomodulation Therapy (PBMT), in all 48 (100%) cases, cerebral blood supply and microcirculation improved, cerebral involutive and atrophic changes decreased. Patients showed persistently decreasing dementia, cognitive and mental abilities improvement. The vast majority began to correspond to the group with a milder disease stage.

Test Group 2. Due to angiogenesis and neurogenesis stimulation, all 14 (100%) cases demonstrated stable dementia reduction, restoration of cognitive, mental functions and daily life activities.

Conclusion: Transcatheter Intracerebral Laser Photobiomodulation Therapy (PBMT) is an effective, physiologically based method of stimulating cerebral angiogenesis and neurogenesis for Alzheimer's Disease and Binswanger's Disease patients. Due to complex laser exposure, patients show cerebral collateral and capillary revascularization, tissue metabolism improvement and cerebral regenerative processes development. Clinically, this leads to stable dementia level decrease, cognitive functions restoration and improvement in patients' quality of life. The resulting clinical effect lasts for many years.

Keywords: Alzheimer's Disease; AD; Binswanger's Disease; BD; PBMT; Transcatheter Intracerebral Laser Photobiomodulation Therapy; Angiogenesis; Neurogenesis.

Introduction:

In connection with the growing life span, dynamic aging of the population is going on, which leads to an increase in cerebral neurodegenerative and ischemic lesions. In turn, it increases the frequency of dementia, cognitive, mental and movement disorders[1,2]. Among neurodegenerative diseases, Alzheimer's disease (AD) steadily occupies the first place. 60% - 80% of all cases of dementia are related to AD. In 2022, only in the United States, the number of patients suffering from this disease amounted to 6.5 million people. These data apply only to patients aged 65 and older. It is estimated that by 2060 the number of patients with AD may increase to 13.8 million people in the US. It should be noted that younger patients were not taken into account[3].

The development of AD has a complex structure; despite numerous studies, the etiology and pathogenesis of this disease are not fully understood[4]. Many studies on the causes of AD have shown that this disease occurs not only as a result of impaired metabolism of amyloid beta (Aβ) and tau protein, but also as a result of the development of the specific cerebral small vessel disease (CSVD) [4-18]. Vascular disorders during AD are manifested in reduction of the capillary bed, development of arteriovenous shunts, and early discharge of arterial blood into the venous bed, followed by venous blood stasis. These changes occur only during AD and have been termed dyscirculatory angiopathy of Alzheimer's type (DAAT) [7, 18]. DAAT appears many years before the clinical signs of the disease, and is obviously congenital in nature [17, 18].

These cerebrovascular changes lead to a specific decrease in intracerebral microcirculation, the development of hypoperfusion and hypoxia, which contributes to neurodegeneration and the development of atrophic changes [7, 8, 18]. At the same time, against the background of specific microvascular changes, patients' Aβ metabolism is disturbed, which leads to a decrease in its excretion and increases its accumulation. Consequently, the amount of Aβ constantly increases in the cerebral tissue and vascular wall[8]. Together, these disorders lead to the damage to the neurovascular unit (NVU) [19]. In the cells of the smooth endoplasmic reticulum and the Golgi apparatus, mitochondria die, synapses are destroyed, degeneration and death of neurons occur [5-9, 11-13, 16, 18-20]. The process is accompanied by a disorder in the permeability of the blood-brain barrier (BBB) [8, 19-21]. These pathological processes are inextricably linked, they exacerbate each other and lead to cerebral dysfunction, neurodegeneration and local, and, further, general cerebral atrophy [7, 9, 12-14,18].

Binswanger's disease (BD) used to be a fairly rare disease. At present, the frequency of this disease has increased significantly and has begun to reach up to 30% of all types of dementia. The etiology of BD has also not been studied in full[22-24]. This disease develops its own specific Cerebral small vessel disease (CSVD), which is manifested by subcortical, atherosclerotic lesions of small arterial branches, arterioles and capillaries of the cerebral white matter[6,22,24-28]. In this BD-specific microcirculatory lesion, the cerebral venous system is less affected than in AD. Patients have small subcortical arteriovenous shunts that do not result in venous congestion[27,28].

BD and subcortical CSVD develop in old age. The process leads to progressive hypoxia, ischemia, and impaired adenosine triphosphate (ATP) metabolism in neuronal mitochondria. This development of the disease firstly causes the death of individual neurons and then their groups. Patients develop focal gliosis, which gradually progresses to widespread gliosis and the development of leukoaraiosis[24-26]. In BD, widespread subcortical demyelization causes cerebral atrophy, cognitive, mental, motor impairment, and dementia [6,24,25, 27,28].

AD and BD have different etiology and pathogenesis; however, these diseases affect the cerebral microvasculature, though in different ways. As a result, patients progressively develop cerebral neurodegeneration in various ways[27].

The treatment of such multicomponent cerebral lesions is a complex task. It requires an integrated approach to the treatment. A great achievement in the development of new methods for the treatment of neurodegenerative and ischemic cerebral lesions was the use of laser energy with low output power in the red or near-infrared region of the spectrum (600-1100 nm). This direction of studies has been termed Laser Photobiomodulation Therapy (PBMT) [29-32].

The energy of laser with low output power in the red or near-infrared region of the spectrum does not have a negative effect on cerebral tissues[32,33]. Numerous experimental and clinical studies have shown that the energy of laser with low output power has a multicomponent effect on the brain. PBMT stimulates angiogenesis, improves blood circulation, restores metabolic processes, stimulates neurogenesis and causes regeneration of cerebral tissues. Clinically, such a complex effect is manifested by an improvement in

cognitive, mental, motor functions and a decrease in dementia[31-34].

According to the mode of laser energy conduction, PBMT is subdivided into transcranial[30-32,34], intranasal (often in combination with transcranial)[35,36], intravenous[37] and transcatheter intracerebral treatment methods[28].

In our earlier studies, we showed that Transcatheter Intracerebral Laser Photobiomodulation Therapy (PBMT) actively stimulates cerebral angiogenesis and neurogenesis in AD and BD[28]. This leads to cerebral revascularization and regeneration of cerebral tissue. As a result, cognitive and mental disorders decrease and dementia regresses. No similar positive result was observed in control groups of patients who received conservative treatment [17,25,28,38].

The present study compares the therapeutic effect obtained after Transcatheter Intracerebral Laser Photobiomodulation Therapy (PBMT) in patients suffering from Alzheimer's Disease and Binswanger's Disease.

Methods

In this study, all examinations and intracerebral transcatheter laser treatments were performed with the written consent of the patients and their relatives, as well as with the approval of The Ethical Review Board (ERB) (Protocol No. 3 of 01-12-2003, Protocol No. 12 of 04 -30-2014).

The study included Alzheimer's Disease and Binswanger's Disease patients who underwent Transcatheter Intracerebral Laser Photobiomodulation Therapy (PBMT) between 2003 and 2015.

The criteria for selecting patients were:

- consent of patients and/or their relatives for the examination and treatment;
- absence of concomitant diseases that could interfere with the examination and treatment;
- satisfactory somatic condition, which made the examination and treatment possible;
- previous diagnosis of Alzheimer's Disease and Binswanger's Disease, as well as signs of dementia and cognitive disorders corresponding to these diseases;
- cerebral involutive and microcirculatory changes corresponding to Alzheimer's Disease and Binswanger's Disease;

Examinations were carried out immediately upon patients' admission to the clinic. Follow-up control was carried out for 8-10 years.

62 patients suffering from Alzheimer's disease and Binswanger's disease with dementia of varying severity and aged from 34 to 81 (mean age 72.75) were selected, of whom men comprised 25 (40.32%), women - 37 (59.68%).

The patients were divided into:

Test group 1: 48 patients with AD aged from 34 to 80 (mean age 67.5), men - 17 (35.42%), women - 31 (54.58%). According to the severity of dementia, the patients were subdivided: preclinical stage (TDR-0 dementia level) - 4, mild stage (TDR-1 dementia level) - 16, moderately severe stage (TDR-2 dementia level) - 21, severe stage (TDR-3 dementia level) - 7.

Test group 2: 14 patients with BD aged from 58 to 81 (mean age 78), men - 8 (57.14%), women - 6 (42.86%). According to the severity of dementia, the patients were subdivided: mild stage (CDR-1 dementia level) - 9, moderately severe stage (CDR-2 dementia level) - 5.

The resulting data were processed statistically using the Statsoft Statistica 10 software (StatSoft Inc., USA). In test group 1 and test group 2, a contingency table analysis was made by means of the Chi-square test to compare the characteristics of Before / After treatment.

Patient examination plan

During the examination, the following was accomplished:

- Clinical severity of dementia was assessed using The Clinical Dementia Rating scale (CDR) [39];
- Cognitive impairment was assessed by the Mini-Mental State Examination (MMSE) [40];
- Cerebral blood flow and microcirculation were assessed by scintigraphy (SG) (the examination was carried out in static and dynamic modes);
- Cerebral perfusion blood filling was assessed by rheoencephalography (REG);
- Laboratory examination was carried out in accordance with the requirements of interventional neuroangiology;
  (All of these examinations were carried out upon admission and discharge of the patient, and then at intervals of 6-12 months);
- Structural cerebral changes were assessed by means of CT and MRI. In patients of test group 1, the digital morphometric scale "The Tomography Dementia Rating scale" (TDR) [41,42] was used to determine the stage of dementia. (CT and MRI for all patients were performed on admission, and subsequently at

intervals of 6-12 months). The examinations were carried out in independent laboratories;

- The condition of the intracerebral vascular and microvasculature bed was assessed using cerebral multi-gated angiography (MUGA), with digital image processing "Angio Vision" [43,44]. The primary examination was performed upon the admission of the patient, the subsequent - immediately after PBMT. In the remote period, MUGA was carried out with a period of 2 to 10 years. In some cases, MSCT angiography (MSCTA) or MR angiography (MRA) were performed.

The results of the examinations are presented in Table 1.

Table1: Results of patient examination.

CHARACTERISTIC OF IDENTIFIED CHANGES	Test Group1 N - 48	Test Group2 N - 14
Clinical Dementia Determination		
CDR – 1	16	9
CDR – 2	21	5
CDR – 3	7	0
Cognitive Disorders		
Decrease to 26-28 MMSE points	4	0
Decrease to 20-25 MMSE points	16	10
Decrease to 12-19 MMSE points	21	4
Decrease to 7-11 MMSE points	7	0
Morphometric determination of dementia stages on the TDR scale according to CT and MRI data		
TDR – 0 (temporal lobes atrophy 4-8%)	4	0
TDR – 1 (temporal lobes atrophy 9-18%)	16	0
TDR – 2 (temporal lobes atrophy 19-32%)	21	0
TDR – 3 (temporal lobes atrophy 33-62%)	7	0
Assessment of cerebral blood flow according to SG data		
Decreased blood flow in cerebral hemispheres	48	14
Assessment of cerebral perfusion blood supply according to REG data		
Decreased volumetric pulse blood supply	48	14
Assessment of intracerebral vascular changes according to MUGA		
Atherosclerotic changes of intracerebral arteries	0	14
Calcium salts deposition in the vascular wall	0	13
Reduction of capillaries in temporal regions	48	0
Development of hypovascular zones in temporal regions	48	0
Decrease in arterial inflow in temporal regions	48	0
Development of arteriovenous shunts in temporal regions	48	0
Development of venous stasis and impaired venous outflow	44	0
Development of increased tortuosity of intracerebral arteries	38	0
Disseminated decrease in the density of subcortical cerebral capillary blood flow	0	14
Multiple disseminated subcortical arteriovenous shunts	0	14

Treatment Method

In a specialized cath lab, all patients from Test Group 1 and Test Group 2 underwent Transcatheter Intracerebral Laser Photobiomodulation Therapy (PBMT) [25,28,38,43,44]. A helium-neon laser ULF-01 (Russia) with a wavelength of 632.8 nm was used as a source of laser exposure. With transcatheter intracerebral conduction, the depth of penetration of laser energy into cerebral tissues was 20-40 mm[45].

After Transcatheter Intracerebral Laser PBMT, disaggregation, anticoagulant, antioxidant, vasodilator and nootropic therapy was performed. Patients received Aspirin, according to the parameters of the blood coagulation system, Heparin and indirect anticoagulants. Infusionally, they received Pentoxifylline 100 mg, Complamin 150 mg, Inosin 200 mg, Nootropil (Piracetam) 1200 mg (or Gliatilin 1000 mg). The number of infusions was 10-15; then they were followed by a

transition to peroral forms. In the subsequent period, courses of tablets were repeated 2 times a year. Test Group 1 patients did not receive the specific therapy intended for the treatment of AD.

Results

Test Group 1.

Immediate results.

When performing cerebral MUGA, immediately after Transcatheter Intracerebral Laser PBMT, a good angiographic result, manifested by pronounced angiogenesis, collateral and capillary revascularization, was obtained in all 48 (100%) cases (Fig. 1(A), Fig.1(B), Fig. 1(C)).

There were no complications after Transcatheter Intracerebral Laser PBMT.

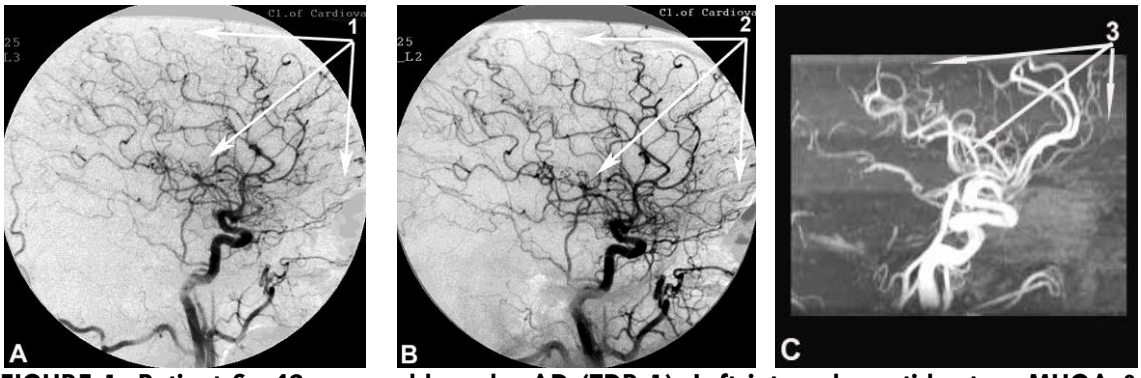


FIGURE 1. Patient S., 42 years old, male, AD (TDR-1): Left internal carotid artery MUGA & MRA before and after transcatheter intracerebral laser PBMT.

A - MUGA. Arterial phase before transcatheter intracerebral laser PBMT.

1 - Hypovascular areas in temporal and frontoparietal regions.

B - MUGA. Arterial phase after transcatheter intracerebral laser PBMT.

2 - Stimulation of angiogenesis, collateral and capillary bed recovery in temporal and frontoparietal region.

C - MRA 10 years after transcatheter intracerebral laser PBMT.

3 - Stimulation of angiogenesis, normal blood supply to the brain.

Early period (1-6 months) after Transcatheter Intracerebral Laser PBMT

- CT and MRI:
  Regardless of the stage of AD, signs of an increase in the volume of normal tissue of the temporal lobes, narrowing of the Sylvian fissures, and contraction of the subarachnoid space were detected in 48 (100%) cases.
- SG and REG:
  Regardless of the stage of AD, signs of restoration of cerebral blood flow velocity and pulse blood filling in the cerebral hemispheres were detected in 48 (100%) cases.
- Clinically:
  Regardless of the stage of AD, signs of positive dynamics, manifested by improved memory, a decrease in the level of dementia, and an improvement in cognitive functions, were detected in 48 (100%) cases. In patients with preclinical AD (TDR-0), recovery of cognitive functions to the level of 28-30 MMSE points was detected in 4 (100%) cases. In patients with mild AD (TDR-1), improvement in cognitive functions to the level of 25-26 MMSE points was detected in 6 (37.50%) cases, to the level of 27-28 MMSE points was detected in 10 (62.50%) cases. In patients with a moderately severe stage of AD (TDR-2), improvement in cognitive functions to the level of 19-20 MMSE points was detected in 12 (57.14%) cases, to the level of 21-22 MMSE points was detected in 9 (42.86%) cases. In patients with severe AD stage (TDR-3), signs of positive dynamics, manifested by a decrease in the level of dementia and an improvement in cognitive functions to the level of 11-12 MMSE points, was detected in 7 (100%) cases.

Long-term follow-up (1-10 years) after Transcatheter Intracerebral Laser PBMT

- CT and MRI:
  In patients with a preclinical AD stage (TDR-0), 1 year after PBMT, recovery of the volume of the normal tissue of the temporal lobes to the age norm, narrowing of the

Sylvian fissures, and recovery of the subarachnoid space were detected in 4 (100%) cases. The resulting positive dynamics persisted throughout the entire observation period in 4 (100%) cases.

In patients with a mild AD stage (TDR-1), 1 year after PBMT, a decrease in the atrophy of the temporal lobes by 8-10%, narrowing of the Sylvian fissures, and a decrease in the subarachnoid space were detected in 16 (100%) cases. In 2-4 years, a further decrease in atrophic changes by another 4-5.5%, almost complete restoration of the normal tissue of the temporal lobes to the age norm were detected in 13 (81.25%) cases (Fig. 2(A), Fig. 2(B), Fig. 2(C), Fig. 2(D)). No further clearly pronounced decrease in atrophic changes was detected in 3 (18.75%) cases. The resulting positive dynamics persisted throughout the entire observation period in 16 (100%) cases.

In patients with a moderately severe AD stage (TDR-2), 1 year after PBMT, a decrease in the atrophy of the temporal lobes by 5-10%, narrowing of the Sylvian fissures, and a decrease in the subarachnoid space were detected in 21 (100%) cases. In 2-3 years, a further decrease in the atrophy of the temporal lobes by another 4-5.5% was detected in 12 (57.14%) cases. No further decrease in involutive changes was found in 9 (42.86%) cases.

In patients with a severe AD stage (TDR-3), 1 year after PBMT, a decrease in the atrophy of the temporal lobes, narrowing of the Sylvian fissures and subarachnoid space were detected in 7 (100%) cases. Of these, a decrease in the atrophy by 10-12% was detected in 5 (71.43%) cases, by 6-8% was detected in 2 (28.57%) cases.

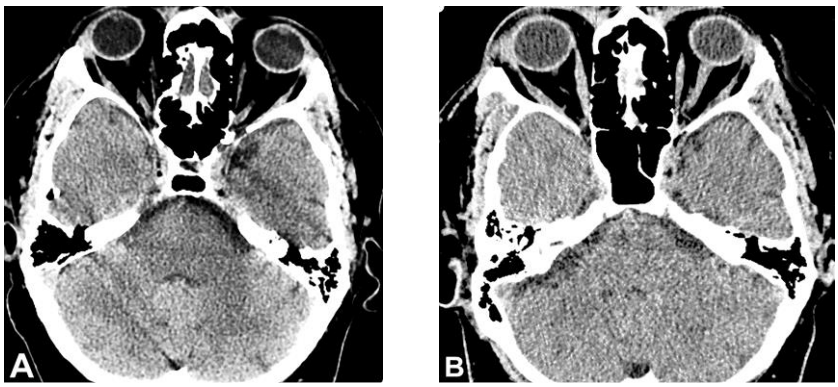
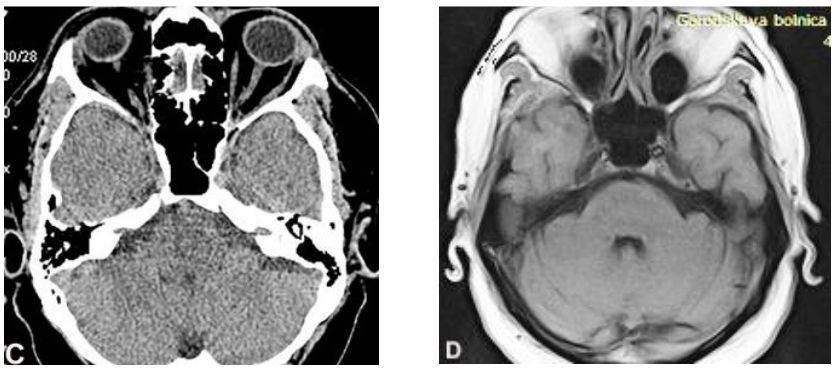


FIGURE 2. The same patient S., 42 years old, male, AD (TDR-1): CT and MRI of the brain before and after transcatheter intracerebral laser PBMT.

A - Cerebral CT before transcatheter intracerebral laser PBMT: Total atrophy of the temporal lobes is 18% of the total tissue volume (dementia level TDR-1).

B - Cerebral CT 1 year after transcatheter intracerebral laser PBMT: total atrophy of the temporal lobes decreased to 9% of the total tissue volume (dementia level TDR-1).



C - Cerebral CT 4 years after transcatheter intracerebral laser PBMT: total atrophy of the temporal lobes decreased to 5.5% of the total tissue volume. The patient is transferred to AD group of TDR-0 stage.

D - Cerebral MRI 10 years after transcatheter intracerebral laser PBMT: total atrophy of the temporal lobes decreased to 5% of the total tissue volume (dementia level TDR-0).

- SG and REG:
  In patients with a preclinical AD stage (TDR-0), 1 year after PBMT, normalization of cerebral blood flow velocity and pulse blood filling was detected in 4 (100%) cases. The resulting positive dynamics persisted throughout the entire observation period in 4 (100%) cases.
  In patients with a mild AD stage (TDR-1), 1 year after PBMT, normalization of cerebral blood flow velocity and pulse blood filling was detected in 16 (100%) cases. The resulting positive dynamics persisted throughout the entire observation period in 16 (100%) cases.
  In patients with a moderately severe AD stage (TDR-2), 1 year after PBMT, positive changes in cerebral blood flow velocity and pulse blood filling were detected in 21 (100%) cases. In the further follow-up period, the obtained positive dynamics persisted in 21 (100%) cases.
  In patients with a severe AD stage (TDR-3), 1 year after PBMT, an improvement in cerebral blood flow velocity and pulse blood filling was detected in 7 (100%) cases.
- Clinically:
  In patients with a preclinical AD stage (TDR-0), 1 year after PBMT, persistent positive dynamics, complete recovery of memory and cognitive functions to the level of 28-30 MMSE points were detected in 4 (100%) cases. The resulting positive dynamics persisted throughout the entire observation period in 4 (100%) cases. Consequently, all 4 (100%) patients were recognized as practically healthy people without dementia and cognitive disorders (Table. 2).
  In patients with a mild AD stage (TDR-1), 1 year after PBMT, persistent positive dynamics, no signs of dementia, recovery of cognitive functions to the level of 27-28 MMSE points were detected in 16 (100%) cases. The resulting positive dynamics persisted throughout the entire observation period in 16 (100%) cases. As a result, all 16 (100%) patients, according to the criteria, began to belong to group TDR-0 (Table. 2).
  In patients with a moderately severe AD stage (TDR-2), 1 year after PBMT, persistent positive dynamics, a decrease in the level of dementia and an improvement in cognitive functions to the level of 21-22 MMSE points were detected in 21 (100%) cases. In 2-3 years, a further decrease in the level of dementia and restoration of cognitive functions to the level of 23-25 MMSE points were detected in 12 (57.14%) cases. Cognitive functions remained at the same level of 21-22 MMSE points in 9 (42.86%) cases. Consequently, 16 (76.19%) patients, in accordance with the criteria, began to belong to group TDR-1, 5 (23.81%) patients remained in group TDR-2 (Table 2). 4 years after the treatment, there was a tendency to a gradual decrease in cognitive functions in 21 (100%) cases.
  In patients with a severe AD stage (TDR-3), 1 year after PBMT, persistent positive dynamics, a decrease in the level of dementia were detected in 7 (100%) cases. Cognitive functions improved to the level of 11-14 MMSE points in 4 (57.14%) cases, to the level of 15-19 MMSE points in 3 (42.86%) cases. Consequently, 5 (71.43%) patients, in accordance with the criteria, began to belong to group TDR-2, 2 (28.57%) patients remained in group TDR-3 (Table 2). 2-2.5 years after the treatment, there was a tendency to a gradual decrease in cognitive functions and an increase in dementia in 7 (100%) cases.

In Test Group 1, repeated cerebral MUGA, MSCTA, or MRA were performed in 10 (20.83%) cases between 2 and 10 years after transcatheter intracerebral PBMT. Retention, as well as further progression of angiogenesis, accompanied by cerebral collateral and capillary revascularization, were detected in 10 (100%) cases (Fig. 1(B), Fig.1(C).

Test Group 2.

Immediate results.

When performing cerebral MUGA, immediately after Transcatheter Intracerebral Laser PBMT, a good angiographic result, manifested by pronounced angiogenesis, collateral and capillary revascularization, was obtained in all 14 (100%) cases (Fig. 3 (A), Fig. 3 (B), Fig. 3(C), Fig. 3(D)).

There were no complications after Transcatheter Intracerebral Laser PBMT.

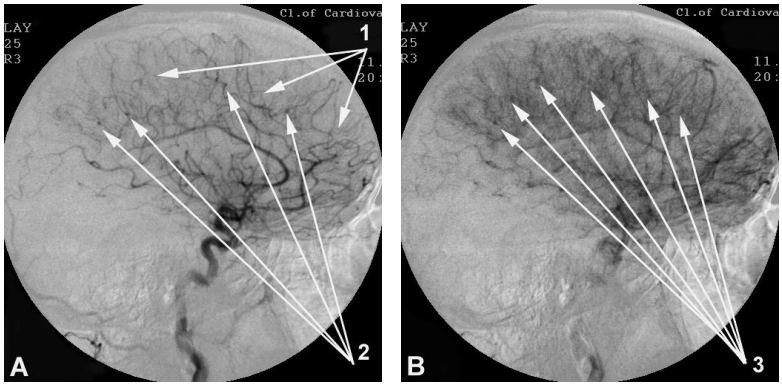


FIGURE 3. Patient I., 74 years old, male, BD (CDR-1): Right internal carotid artery MUGA before and after transcatheter intracerebral laser PBMT.

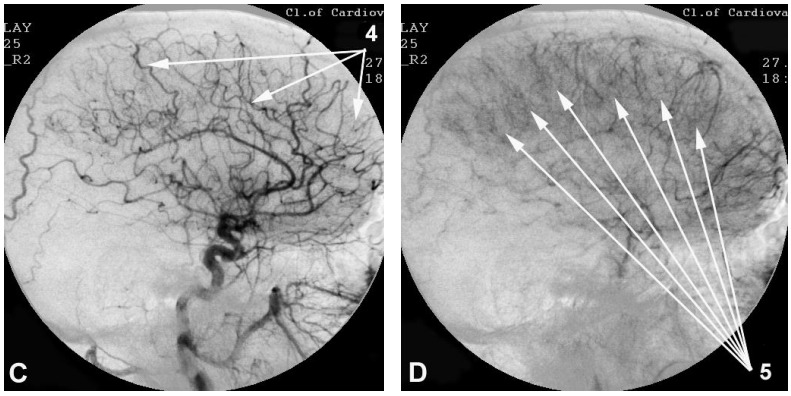
A - Arterial phase before transcatheter intracerebral laser PBMT.

1 - Depletion of the capillary bed of the brain white matter.

2 - Multiple subcortical arteriovenous shunts.

B - Venous phase before transcatheter intracerebral laser PBMT.

3 - Multiple subcortical arteriovenous shunts.



C - Arterial phase after transcatheter intracerebral laser PBMT.

4 - Stimulation of angiogenesis, collateral arterial and capillary bed restoration.

D - Venous phase after transcatheter intracerebral laser PBMT.

5 - Closing of multiple arteriovenous shunts.

Early period (1-6 months) after Transcatheter Intracerebral Laser PBMT

- CT and MRI:
  Signs of a decrease in general cerebral involutive changes, narrowing of the subarachnoid space were detected in 14 (100%) cases.
- SG and REG:
  Improvement in the rate of cerebral blood flow and pulse blood filling in the hemispheres was detected in 14 (100%) cases.
- Clinically:
  positive dynamics, manifested by improvement in cognitive, mental, motor functions and a decrease in dementia, was detected in 14 (100%) cases.

Long-term follow-up (1-8 years) after Transcatheter Intracerebral Laser PBMT

- CT and MRI:
  1 year after PBMT, regardless of the stage of dementia, a progressive decrease in total cerebral involutive and atrophic changes was detected in 14 (100%) cases. After 2 years, a further decrease in involutive and atrophic changes was detected in 14 (100%) cases. Narrowing of the Sylvian fissures was detected in 13 (92.86%) cases. A decrease in the signs of non-occlusive hydrocephalus was found in 6 (42.97%) cases. Gliosis decreased in 9 (64.29%) cases. Signs of leukoaraiosis

decreased in 3 (21.43%) cases. The resulting positive dynamics persisted throughout the entire observation period in 14 (100%) cases.

- SG and REG:
  One year after PBMT, a pronounced improvement in the rate of cerebral blood flow and pulse blood filling was detected in 14 (100%) cases. The resulting positive dynamics persisted throughout the entire observation period in 14 (100%) cases.
- Clinically:
  1-2 years after PBMT, regardless of the stage of dementia, persistent positive dynamics, a significant decrease in signs of dementia, recovery of cognitive functions to the level of 25-29 MMSE points were detected in 14 (100%) cases (Table. 2). The resulting positive dynamics persisted throughout the entire observation period in 14 (100%) cases.

In Test Group 2, repeated cerebral MUGA, MSCTA, or MRA were performed in 8 (57.14%) cases between 2 and 8 years after transcatheter intracerebral PBMT. Retention, as well as further progression of angiogenesis, accompanied by cerebral collateral and capillary revascularization, were obtained in 8 (100%) cases.

Table 2: Dynamics of changes in the severity of dementia and cognitive impairment in patients of Test Group 1 and Test Group 2 in the long-term period after the treatment

Signs of dementia and cognitive impairment	**Test Group 1 Before treatment N-48**	**Test Group 1 After treatment N-48**	**p (chi-square)**
Practically healthy MMSE - 29-30 points	**0**	**4**	**P=0.00130**
TDR-0, MMSE - 26-28 points	**4**	**16**	
TDR-1, MMSE - 20-25 points	**16**	**16**	
TDR-2, MMSE - 12-19 points	**21**	**10**	
TDR-3, MMSE - 7-11 points	**7**	**2**	
	Test Group 2 Before treatment N-14	**Test Group 2 After treatment N-14**	**P=0.000053**
Practically healthy MMSE - 29-30 points	**0**	**9**	
CDR-1, MMSE - 20-25 points	**9**	**5**	
CDR-2, MMSE - 12-19 points	**5**	**0**	

Post-treatment indicators were significantly different from pre-treatment ones in each group ($p<0.05$).
Statistical significance of results in Test group 1 ($p=0.00130$).
Statistical significance of results in Test group 2 ($p=0.000053$).

Discussion

Pathogenetically, cerebral microcirculatory disorders that develop in AD and BD have different etiologies and are located in different cerebral regions.

In patients with AD, reduction of arterioles and capillaries takes place in the temporal lobes, and then in the fronto-parietal cerebral regions. It is highly likely that this lesion is congenital in nature[17,18]. The process is accompanied by impaired Aβ metabolism and its accumulation in the cerebral tissue and vascular wall[8,19].

BD develops at a more mature age; this disease is not congenital. It affects the subcortical arterioles and capillaries of the cerebral white matter. The lesion has a sclerotic character [22,25].

These diseases are united by the fact that in both cases the developed disorders of microcirculation lead to specific hypoperfusion, hypoxia, disruption of metabolic processes in neurons, neuronal death, subsequent demyelization, and cerebral neurodegeneration [6,12,20-23,25].

The mechanism of action on cerebral tissues during transcatheter intracerebral PBMT using laser with low output power is multicomponent and complex[29-34].

Due to transcatheter intracerebral exposure, the amount of laser energy penetrating into cerebral tissues is higher than with other methods of PBMT, which makes only one intervention possible. Due to morphological features, the depth of propagation of the energy of a helium-neon laser with a wavelength of 632.8 nm in cerebral tissues is about 20-40 mm [45]. Not only blood, the vascular wall and directly located tissues are exposed to laser exposure, but also more distant cerebral regions.

Examination of patients from Test Group 1 and Test Group 2 over a long period of observation showed that laser energy has a multifaceted effect on the brain.

Laser exposure stimulates angiogenesis, causes a rapid opening of the arterial collateral and capillary bed, which leads to cerebral revascularization (Fig.1(A), Fig.1(B), Fig.3(A), Fig.3(C)). The process of revascularization develops not only in the tissues located in the immediate vicinity of the laser exposure, but also in more distant cerebral regions. The restored capillary blood supply improves oxygenation and nutrition of cerebral tissues. At the same time, pathological arteriovenous shunts that appeared during the development of DAAT are closed. As a result, venous outflow of blood is normalized in patients. Recovery of capillary inflow of arterial blood and venous outflow improves the process of excretion of Aβ from cerebral tissues and contributes to the normalization of its metabolism.

Against the background of improved blood supply, laser energy affects neurons, stimulates ATP metabolism in them and causes recovery of cellular and tissue metabolism.

With improved capillary blood supply, activation of cellular and tissue metabolism, laser energy stimulates neurogenesis and causes regeneration and recovery of normal cerebral tissues (Fig. 2(A), 2(B), 2(C)).

Together, all these processes lead to a decrease in cerebral involutive and atrophic changes. Clinically, it is manifested by the restoration of cognitive and mental functions and a decrease in the level of dementia.

The combination of these complex recovery processes made it possible to transfer Test Group 1 patients with a preclinical AD stage and dementia severity of TDR-0 into the category of apparently healthy people without dementia. Patients with a mild AD stage of TDR-1 – to transfer to a preclinical AD stage of TDR-0. Also, in the vast majority of cases, to transfer patients with a moderately severe AD stage of TDR-2 to a mild AD stage of TDR-1, and patients with a severe AD stage of TDR-3 to a moderately severe AD stage of TDR-2 (Table 2).

Despite the sclerotic nature of the capillary lesion in patients of Test Group 2, transcatheter intracerebral PBMT also caused a pronounced stimulation of cerebral angiogenesis. The process was accompanied by the opening of arterial and capillary collateral branches of the subcortical regions (Fig. 3(A), 3(C)). As a result, the blood supply of white cerebral matter improved, which reduced hypoxia and ischemia and led to the closure of arteriovenous shunts (Fig. 3(B), Fig. 3D)). Laser energy improved and normalized the metabolic processes in the cerebral tissue, caused stimulation of neurogenesis and the regeneration of normal cerebral tissues.

Such a complex action led to a pronounced, persistent improvement of cognitive, mental functions and a decrease of dementia in all patients in Test group 2 (Table 2).

This study showed that when PBMT is carried out, the stimulation of angiogenesis and neurogenesis does not depend on the nature of a microcirculatory lesion and develops in various cerebral regions.

A positive effect was obtained after transcatheter intracerebral laser PBMT both in patients from Test group 1 and in patients from Test group 2, and can be observed for years.

Considering the difference in the effect of transcatheter intracerebral laser PBMT, it should be noted that in patients of Test group 1, the first positive reaction after transcatheter intracerebral laser PBMT appeared earlier than in patients of Test group 2. 1-2 days after the treatment, patients of Test group 1 showed signs of recovery of mental, cognitive functions and improved logical thinking. In patients of test group 2, a similar reaction developed on days 3-4.

The results obtained in this work are confirmed by numerous experimental and clinical studies by other authors, which have shown high efficiency of using laser with low output power to stimulate angiogenesis and neurogenesis during transcranial, intranasal and intravenous photobiomodulation therapy in patients with ischemic, neurodegenerative and traumatic cerebral lesions accompanied by dementia[29-37].

Moreover, the data presented in this study illustrate and decipher the mechanism of stimulation of angiogenesis and neurogenesis when brain tissue is exposed to laser energy with low output power of the red spectral region.

Conclusions

Intracerebral transcatheter laser PBMT is a pathogenetically substantiated, effective method for the treatment of cerebral microcirculatory lesions in Alzheimer's Disease and Binswanger's Disease. PBMT is the most physiological treatment method for intracerebral microvascular lesions.

During intracerebral transcatheter PBMT, the energy of laser with low output power in the red region of the spectrum has a complex effect on cerebral tissues. The intervention stimulates angiogenesis, causes collateral and capillary revascularization, restores ATP metabolism in

neurons, improves cellular and tissue metabolism, stimulates neurogenesis, and causes regeneration of tissue structures. The therapeutic effect of PBMT does not depend on the pathoanatomical mechanism of lesions of the cerebral microcirculatory bed.

In patients from Test group 1 and Test group 2 with a different severity of AD and BD, transcatheter intracerebral laser PBMT allowed to significantly recover mental, cognitive functions and to decrease the level of dementia. The treatment carried out led to an improvement in daily life and returned patients to a full active life. The resulting positive clinical effect has been observed for a long time.

Declaration of Conflicting Interests

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