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Results of an international multicenter, randomized, double-blind, placebo-controlled study assessing the efficacy and safety of sequential therapy with Mexidol and Mexidol FORTE 250 in patients with chronic brain ischemia (MEMO)

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Abstract

Objective. To assess the efficacy and safety of sequential therapy with Mexidol solution for intravenous and intramuscular administration, 50 mg/ml and Mexidol FORTE 250 film-coated tablets, 250 mg in patients with chronic brain ischemia (CBI).

Material and methods. An international multicenter, randomized, double-blind, placebo-controlled trial, conducted in 15 clinical centers located In Russian Federation and Republic of Uzbekistan, included 318 patients with CBI aged 40 to 90 years. The patients were randomized into 2 groups, the patients of the 1-st group received Mexidol intravenously 500 mg once daily for 14 days, followed by Mexidol FORTE 250 — 250 mg 3 times a day orally for 60 days; patients of the 2-nd group received a placebo in a similar mode. The primary endpoint was the mean value of difference by MoCA scale at the point of completing the therapy comparing to initial value.

Results. According to the results of the assessment of the primary endpoint, statistically significant changes in the MoCA scores at the stage of completion of study were revealed when comparing the dynamics between the 1-st and 2-nd groups ($p<0.000001$). The lower limit of the 95% confidence interval for the difference in the average of the main efficacy endpoint between the 1-st and 2-nd groups was 1.51, which allows to state a higher efficacy of the use of Mexidol. According to the estimates of secondary endpoints, a statistically significant advantage over placebo at the last visit achieved while evaluation by the following scales and tests: digit symbol substitution test, MFI-20 asthenia assessment scale, Beck anxiety scale, Vane questionnaire, Tinetti scale, SF-36 questionnaire (mental component of health), CGI scale. The comparable nature of the safety profile of Mexidol and Placebo was established.

Conclusion. The validity and expediency of the use of Mexidol and Mexidol FORTE 250 in the treatment of patients with CBI has been demonstrated.

Keywords: *chronic brain ischemia, cognitive impairment, neuropsychological testing, ethylmethylhydroxypyridine succinate, Mexidol, Mexidol FORTE 250, treatment of CBI, MEMO trial.*

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Chronic cerebrovascular diseases, in particular chronic brain ischemia (CBI), are common in the population [1—4]. Cognitive disorders, as well as symptom complexes such as anxiety, depression, asthenia and motor disorders, especially balance and walking disorders, are the most common clinical manifestations of CBI [5—7]. CBI treatment includes pathogenetic and symptomatic therapy [8, 9]. In the comprehensive treatment of patients with CBI, drugs with multimodal action, which contribute to the optimization of cerebral microcirculation and provide neurometabolic protection of neurons in ischemia and hypoxia, are widely used. Nevertheless, the number of randomized trials on the efficacy and safety of drug therapy for CBI is insufficient until today.

Mexidol (ethylmethylhydroxypyridine succinate) is an original Russian antioxidant and antihypoxant, synthesized at the Research Institute of Pharmacology of the Russian Academy of Medical Sciences in the mid-1980s [10]. Mexidol consists of two related and functionally relevant compounds: 2-ethyl-6-methyl-3-hy-

droxypyridine and succinate, the combination of which determines its multimodal properties [10—13]. The main effects of Mexidol are antioxidant, antihypoxic and membrane-stabilizing, as well as reduction of glutamate excitotoxicity [10—14]. Due to their combination, Mexidol has nootropic, anti-amnestic, anxiolytic and other effects [10, 14]. The efficacy of Mexidol in patients with acute and chronic cerebrovascular pathology has been demonstrated in a number of clinical studies [5, 15—18]. The advantages of the drug are the combination of therapeutic index with high safety profile, absence of sedative, myorelaxant, stimulating actions [10, 14, 15].

The study objective was to investigate the efficacy and safety of sequential therapy with Mexidol parenterally and Mexidol FORTE 250 orally in patients with CBI.

Material and Methods

An international multicenter, randomized, double-blind, placebo-controlled study (MEMO study — MExidol — chronic brain ischemia) was carried out in 15 clinical centers located on the territory of the Russian Federation and the Republic of Uzbekistan. The study included 318 patients aged 40—90 years.

Inclusion criteria: established clinical diagnosis of CBI; mild cognitive impairment (MCI) syndrome according to DSM-5; cognitive function estimate on the MoCA scale up to 25 scores inclusive; presence of signs of cerebral vascular lesions according to MRI/CT data; age of clinical signs of CBI from 1 to 5 years.

Non-inclusion cruteria: any diagnosis of the disease less than 6 months prior to inclusion that may cause symptoms similar to the nosology under investigation, acute cerebrovascular accident within 1 year prior to screening, inflammatory, demyelinating brain diseases at the time of screening or in the history, depression level on the Hamilton scale at screening ⩾14 scores, severe cognitive impairment/dementia, psychiatric disorders (except for mild cognitive impairment syndrome), decompensation of somatic diseases at the time of screening, history of intolerance to any of the components of the study drugs, pregnancy, lactation period.

The mean value of the MoCA scale score change at the study completion by patient stage compared to baseline was the primary endpoint. The assessment of dynamics on the Digit symbol substitution test, the MFI-20 subjective asthenia assessment scale, the Beck anxiety scale, the Vane autonomic status scale, the Tinetti balance & gait scale, the SF-36 quality of life questionnaire, and the CGI (Clinical Global Impressions) scale were used as the secondary endpoints. Safety of the therapy was assessed based on the presence and severity of adverse events (AEs) reported during the study.

The study flow diagram included visit 0 (screening period of 7 days or less), visit 1 (initiation of parenteral therapy), visit 2 (completion of parenteral therapy), visit 3 (telephone contact), visit 4 (completion of the 1st month of tablet therapy), visit 5 (final visit). After clinical and neuropsychological examination according to the protocol, group 1 patients received Mexidol intravenously at a dose of 500 mg in 100—200 ml of 0.9% NaCl solution once a day for 14 days, then Mexidol FORTE 250 (film-coated tablets) at a dose of 250 mg 3 times a day for the next 60 days. Group 2 patients received placebo in a similar regimen.

All patients received baseline therapy (antiaggregants, antihypertensive, hypolipidemic and other agents) in unchanged doses and combinations during the previous month.

Statistical processing of the data obtained during the study was carried out using validated specialized software — Tibco Statistica v.13 statistical package.

Results

Distribution of patients into the study groups is presented in **the fig. 1.**

Six patients completed the study prematurely. In group 1, the reasons for premature completion were the patient's inability or refusal to follow the protocol requirements (n=1, 0.6%), withdrawal of informed consent (n=1, 0.6%), in group 2: the patient's inability or refusal to follow protocol requirements (n=1, 0.6%) and withdrawal of informed consent (n=3, 1.9%).

The groups were comparable in terms of baseline patients' characteristics. The baseline characteristics of the patients included in the study are given in **the tab. 1.**

Groups were initially comparable to each other in terms of the studied clinical parameters as well **(Table 2).**

Results and discussion

Efficacy. Primary and secondary endpoints

Statistically significant changes in scores on the MoCA scale at the study completion by patient stage (visit 5) have been revealed when comparing the dynamics between groups 1 and 2 (p<0.000001, t-test for independent samples).

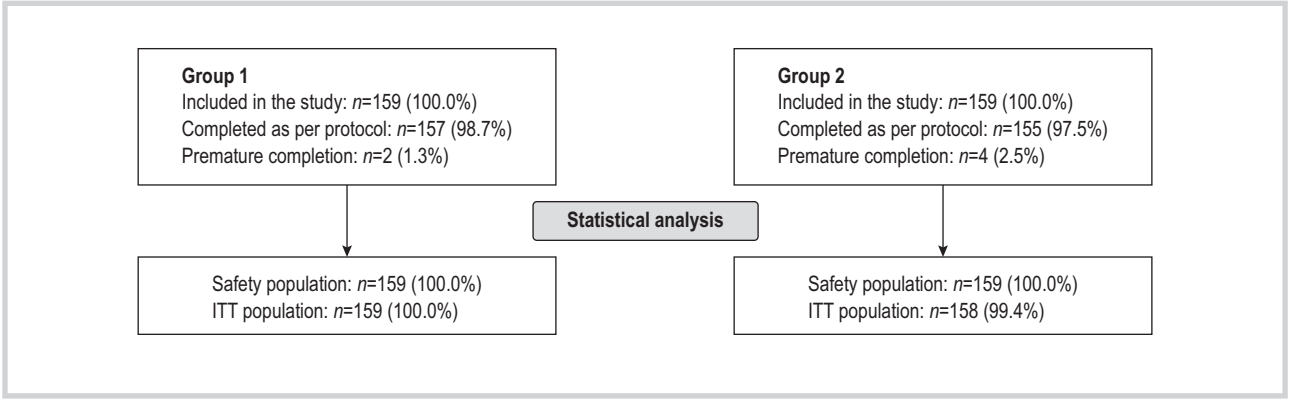

Fig. 1. **Distribution of patients into study groups.**
ITT (English: Intent-to-treat population) — the population according to the prescribed treatment.

Table 1. **Baseline characteristics of patients included in the study**

Indicator	Group 1 (n=159)	Group 2 (n=159)	p
Age, years (Mean±SD)	60.08±9.86	60.73±9.03	0.538[a]
BMI, Me [Q_1; Q_3], kg/m^2	28.08 [25.51; 31.02]	27.47 [25.53; 30.99]	0.818[b]
Sex, *n (%)*			0.794[c]
Male	40 (25.16)	38 (23.90)	
Female	119 (74.84)	121 (76.10)	
Race, *n (%)*			0.627[c]
Caucasian	149 (93.71)	151 (94.97)	
Mongoloid	10 (6.29)	8 (5.03)	

Note. BMI — body mass index; [a] — Student's *t*-test; [b] — Mann—Whitney *U* test, [c] — Pearson's χ^2 test.

Table 2. **Results of the initial examination of patients (ITT population)**

Indicator (score)	Group 1 (n=159)	Group 2 (n=158)	p
MoCA scale, Me [Q_1; Q_3]	22 [20; 23]	22 [21; 23]	0.435[b]
SF-36 questionnaire (physical component of health), Me [Q_1; Q_3]	44 [38; 51]	45 [39; 50]	0.821[b]
SF-36 questionnaire (mental component of health), Me [Q_1; Q_3]	45 [36; 52]	45 [39; 52]	0.528[b]
MFI-20 scale, M±SD	59.8±13.4	58.8±13.8	0.520[a]
Beck anxiety scale, Me [Q_1; Q_3]	9 [6; 16]	9 [6; 14]	0.342[b]
Vane questionnaire, Me [Q_1; Q_3]	26 [16; 36]	24 [17; 36]	0.755[b]
Digit symbol substitution test, Me [Q_1; Q_3]	32 [24; 40]	34 [26; 40]	0.483[b]
Tinetti scale, Me [Q_1; Q_3]	33 [30; 36]	34 [30; 37]	0.248[b]

Note. [a] — Student's *t*-test; [b] — Mann—Whitney *U* test.

Table 3. **Dynamics of values on the MoCA scale between visits 5 and 0**

MoCA scale (scores)	Main population		
	Group 1 (n=157)	Group 2 (n=155)	Mean difference [95% CI] (scores)
Differences in values on the scale between visits 5 and 0	4.22±2.59	2.17±2.20	2.05 [1.51; 2.58]
t-test for independent samples		p<0.000001	

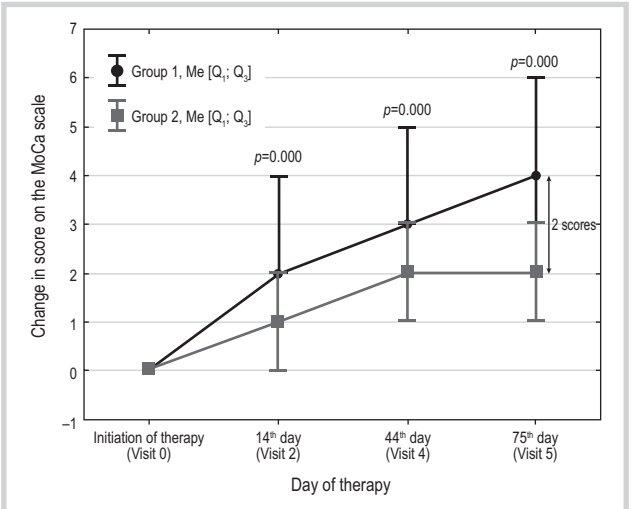

Fig. 2. **Dynamics of MoCA scores compared to the baseline level (medians of the absolute dynamics, 25th and 75th percentiles, p — values Mann—Whitney test).**

The dynamics of the MoCA test between the screening and final visits was 4.22±2.59 scores in group 1 and 2.17±2.20 scores in group 2 (mean difference between the groups — 2.05 scores) according to the results of the primary endpoint study. The lower bound of the 95% confidence interval for the mean difference of the main efficacy endpoint in the groups is a positive value of 1.51, which indicates the superior efficacy of therapy with Mexidol and Mexidol FORTE 250 over placebo **(tab. 3).**

When comparing the median of change in scores on the MoCA scale by visits, statistically significant differences in the dynamics of scores between the groups have been noted starting from the 2nd visit compared with the baseline. Further, an increasing positive dynamics has been noted in group 1 **(fig. 2)** in presence of long-term sequential therapy. In group 2, the median of absolute value did not reach the indicators of the norm when assessed on the MoCA scale at the end of the study, the differences between the groups were statistically significant (p=0.000).

Changes in scores on the Digit symbol substitution test were assessed using the results obtained at visits 2, 4 and 5 compared to those obtained at the randomization visit (visit 1) **(fig. 3).**

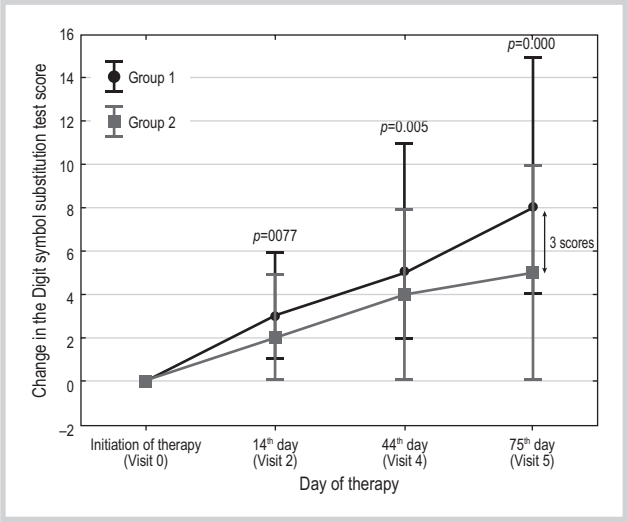

Fig. 3. **Dynamics of scores based on the results of the digital symbol substitution test compared to the baseline level.**
Here and in **fig. 5—8**: medians of the absolute dynamics, 25th and 75th percentiles, *p* — values Man—Whitney test.

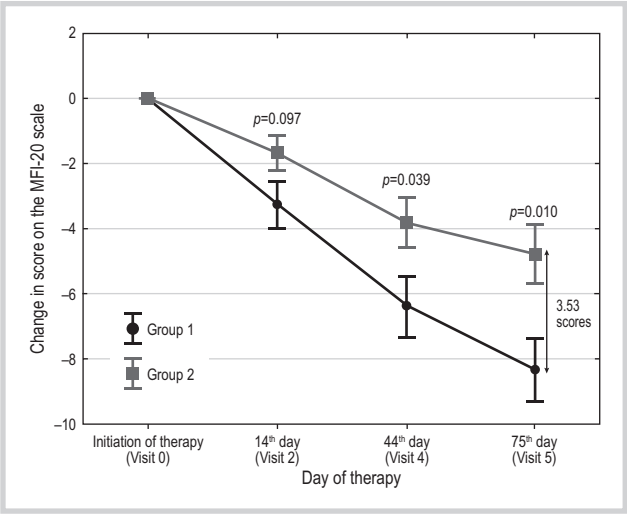

Fig. 4. **Dynamics of scores on the MFI-20 scale compared to the baseline level (mean values of absolute dynamics, 95% confidence intervals, values of Student's *t*-test).**

Statistically significant differences between the groups when comparing medians of the absolute dynamics on the Digit symbol substitution test have already been noted from visit 4 (after 1 month of tablet therapy). The medians of the absolute dynamics of scores on the Digit symbol substitution test at visit 5 compared to the baseline amounted to 8.00 [4.00; 15.00] scores in group 1 and 5.00 [0.00; 10.00] scores in group 2. The differences between the groups were statistically significant (p=0.000). Thus, there is an increasing positive dynamics in assessment on this test in presence of long-term sequential therapy.

Changes in scores on the MFI-20 asthenia scale were assessed using the results obtained at visits 2, 4 and 5 compared to those obtained at the randomization visit (visit 1) **(fig. 4).** The mean values of the absolute dynamics of scores on the MFI-20 asthenia scale on visit 5 compared to the baseline amounted to 8.33±12.68 scores in group 1 and 4.80±11.42 scores

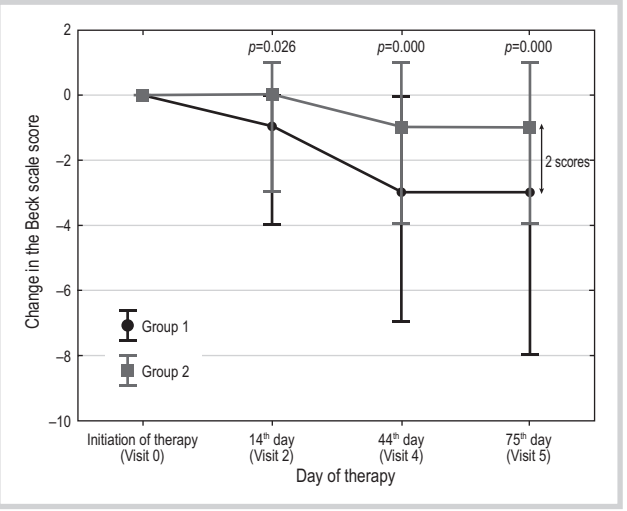

Fig. 5. **Dynamics of scores on the Beck anxiety scale compared to the baseline level.**

in group 2, the differences between the groups were statistically significant (p=0.010).

It has been revealed that statistically significant differences between the groups are already noted from visit 4 (after 1 month of tablet therapy) when comparing the mean values of the absolute dynamics on the MFI-20 asthenia scale. Increasing positive dynamics in assessment on this scale in presence of long-term sequential therapy is also noted.

Changes in assessment on the Beck anxiety scale were evaluated using the results obtained at visits 2, 4 and 5 compared to those obtained at the randomization visit (visit 1) — **(fig. 5).** Despite the fact that the patients included in the study were characterized by a negligible level of anxiety, statistically significant differences between the groups are already noted from visit 2 (completion of parenteral therapy) when comparing the medians of the absolute dynamics on the Beck anxiety scale. Increasing positive dynamics in assessment on the Beck anxiety scale on the background of long-term sequential therapy is noted as well. The medians of the absolute dynamics of scores on the Beck anxiety scale at visit 5 compared to the baseline amounted to −3.00 [−8.00; −1.00] scores in group 1 and −1.00 [−4.00; 1.00] scores in group 2, the differences between the groups were statistically significant (p=0.000).

Changes in assessment on the Vane questionnaire were evaluated using the results obtained at visits 2, 4 and 5 compared to those obtained at the randomization visit (visit 1) **(fig. 6).**

The medians of the absolute dynamics of scores at visit 5 compared to the baseline amounted to −5.00 [−12.00; 0.00] scores in group 1 and −2.00 [−10.00; 0.00] scores in group 2. The differences between the groups were statistically significant (p=0.035).

Changes in assessment on the Tinetti scale were evaluated using the results obtained at visits 2, 4 and 5 compared to those obtained at visit 1 **(fig. 7).**

Statistically significant differences between the groups are already noted from visit 2 (completion of parenteral therapy) when comparing the medians of the absolute dynamics. The medians of the absolute dynamics of scores on the Tinetti scale at visit 5 compared to the baseline amounted to 3.00 [1.00; 5.00] scores in group 1 and 1.00 [0.00; 4.00] scores in group 2. The differences between the groups were statistically significant (p=0.000). Thus,

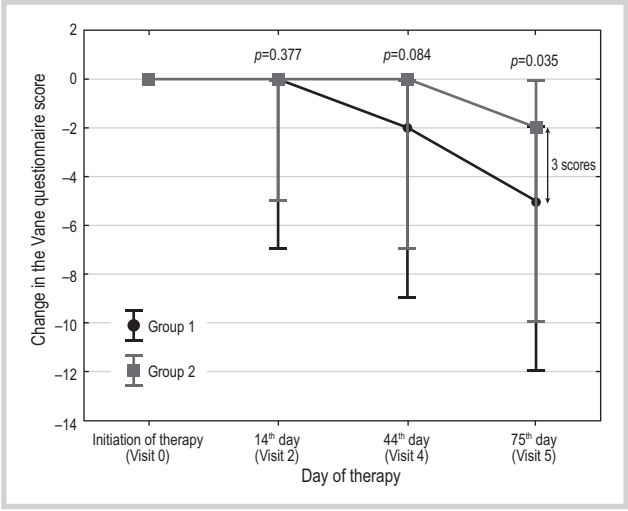

Fig. 6. **Dynamics of points on the Vane questionnaire compared to the baseline level.**

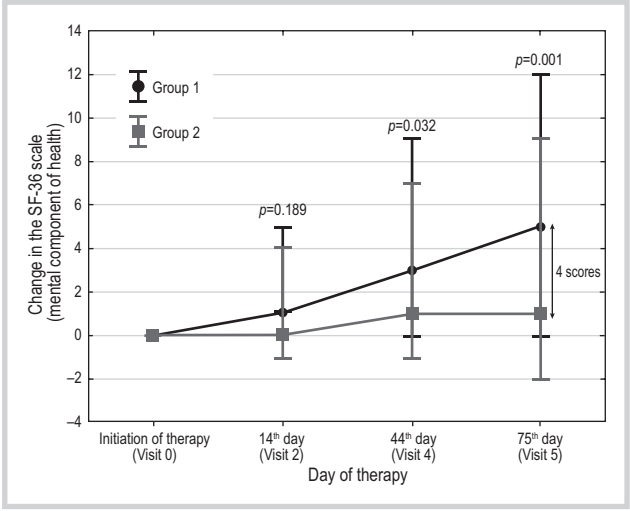

Fig. 8. **Dynamics of scores on the SF-36 questionnaire (mental component of health) compared to the baseline level.**

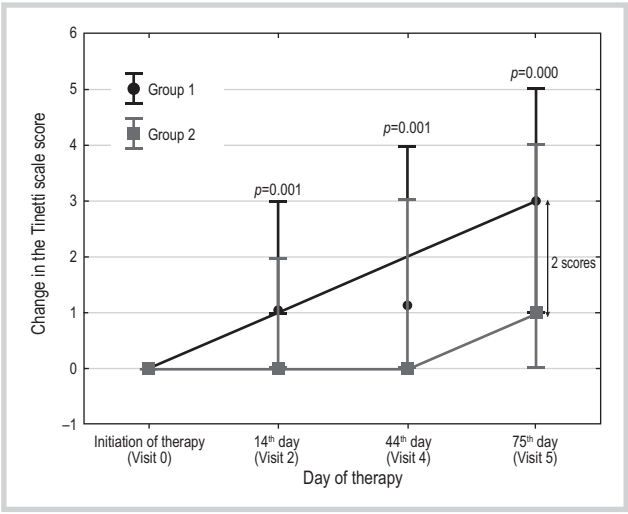

Fig. 7. **Dynamics of scores on the Tinetti scale compared to the baseline level.**

an increasing positive dynamics in assessment on the Tinetti scale in presence of long-term sequential therapy is noted.

Changes in assessment on the SF-36 questionnaire were evaluated using the results obtained at visits 2, 4 and 5 compared to those obtained at visit 1. Physical and mental components were assessed separately. According to the obtained results, a tendency to a higher indicator on the physical component has been noted in group 1, but statistical significance was not achieved compared to group 2.

Statistically significant differences between the groups are already noted from visit 4 (after 1 month of tablet therapy) when comparing the medians of the absolute dynamics on the SF-36 questionnaire (mental component of health) **(fig. 8).** The medians of the absolute dynamics of scores on the SF-36 questionnaire (mental component of health) at visit 5 compared to the baseline amounted to 5.00 [0.00; 12.00] scores in group 1 and 1.00 [−2.00; 9.00] scores in group 2, the differences between the groups were statistically significant (p=0.001). Thus, an increasing positive dynamics in assessment on this questionnaire in presence of long-term sequential therapy is noted.

Dynamics in assessment on the Clinical Global Impression (CGI) scale were evaluated using the results obtained at visits 2 and 5 compared to those obtained at visit 1 **(tab. 4).** Statistically significant differences between the groups were found in assessment on the CGI scale.

Thus, statistically significant differences between the groups when comparing the medians of the absolute dynamics are already noted from visit 2 (completion of parenteral therapy) in assessment on the MoCA scale, Beck anxiety scale, Tinetti balance & gait scale, as well as statistically significant differences between the groups are noted in evaluation on the CGI scale. Statistically significant differences between the groups when comparing the medians of the absolute dynamics are already noted from visit 4 (after 1 month of tablet therapy) in assessment on the Digit symbol substitution test, SF-36 questionnaire (mental component of health). In the same time frame, statistically significant differences between the groups have been noted in comparison of the mean values of the absolute dynamics in assessment on the MFI-20 scale. Statistically significant differences between the groups have been observed at visit 5 when comparing the medians of the absolute dynamics in assessment on the Vane questionnaire. The obtained results indicate the advantage of long-term sequential therapy with Mexidol and Mexidol FORTE 250 over placebo **(see fig. 2—8, tab. 4, 5).**

Safety

A total of 53 AEs, none of which were serious, were reported as a result of the treatment safety analysis. AEs were revealed in 15 (9.43%) patients in group 1 (19 AEs in total) and in 21 (13.21%) in group 2 (34 AEs in total), the differences in the incidence of AEs were statistically insignificant (p=0.288 Pearson's χ^2 test). Relative risk of AE in group 1 amounted to 0.82; 95% CI [0.55; 1.22] compared to group 2. No statistically significant differences were found between the compared groups with regard to the risk of AEs.

All the AEs recorded in the present study were of mild and moderate severity; the majority of AEs (47) corresponded

Table 4. **Statistical analysis of score on the CGI scale**

CGI	Visit 2		Visit 5	
	Group 1	Group 2	Group 1	Group 2
1 (significant improvement, absence of AEs)				
abs.	20	9	45	7
%	12.58	5.73	28.66	4.52
3 (significant improvement, but AEs have a considerable impact on the patient's activities of daily living)				
abs.	2	1	1	0
%	1.26	0.64	0.64	0.00
4 (significant improvement, AEs exceed the therapeutic effect)				
abs.	1	1	0	1
%	0.63	0.64	0.00	0.65
5 (significant improvement, absence of AEs)				
abs.	16	9	39	16
%	10.06	5.73	24.84	10.32
9 (minor improvement, absence of AEs)				
abs.	75	53	54	56
%	47.17	33.76	34.39	36.13
10 (minor improvement, AEs do not significantly affect the patient's activities of daily living)				
abs.	4	2	3	0
%	2.52	1.27	1.91	0.00
11 (minor improvement, AEs have a significant impact on the patient's activities of daily living)				
abs.	1	0	0	0
%	0.63	0.00	0.00	0.00
13 (no change or worsening of condition, absence of AEs)				
abs.	40	82	15	75
%	25.16	52.23	9.55	48.39
Differences between the groups	Pearson's χ^2 test: p=0.000		Pearson's χ^2 test: p=0.000	

Table 5. **Results of evaluation of secondary endpoints**

Indicator (scores)	Values of the difference between indicators at visits 1 and 5		
	Group 1 (n=157)	Group 2 (n=155)	p
Digit symbol substitution test, Me [Q_1; Q_3]	8 [4; 15]	5 [0; 10]	0.000[b]
MFI-20 scale, $M \pm SD$	−8.33±12.68	−4.80±11.42	0.010[a]
Beck anxiety scale, Me [Q_1; Q_3]	−3 [−8; −1]	−1 [−4; 1]	0.000[b]
Vane questionnaire, Me [Q_1; Q_3]	−5 [−12; 0]	−2 [−10; 0]	0.035[b]
Tinetti scale, Me [Q_1; Q_3]	3 [1; 5]	1 [0; 4]	0.000[b]
SF-36 questionnaire (mental component of health), Me [Q_1; Q_3]	5 [0; 12]	1 [−2; 9]	0.001[b]

Note: [a] — Student's *t-test*; [b] — Mann—Whitney *U* test.

to mild severity in both groups. AEs in group 1 (19 (100%)) and in group 2 (28 (82.4%)) AEs were of mild severity, the differences between the groups were statistically insignificant (p=0.077 Fisher's exact test). In the vast majority of cases, AEs resolved on their own (of which 16 (84.2%) in group 1 and 21 (61.8%) in group 2; p=0.223). Summarized information on all registered AEs is given in **the tab. 6.** Results of laboratory assessment and physical examination also indicated that there were no significant differences between the compared groups.

Conclusion

The results of the study convincingly demonstrate high clinical efficacy of long-term sequential therapy with Mexidol and Mexidol FORTE 250 in patients with CBI and safety comparable to placebo. The study proved the superior efficacy of therapy with Mexidol and Mexidol FORTE 250 over placebo.

Statistically significant differences between the groups on the MoCA scale, Beck anxiety scale, Tinetti balance & gait scale, CGI scale have been already determined from the 2nd week

Table 6. **Number of patients with AEs**

Adverse event	Group 1 (n=159)		Group 2 (n=159)		p (Fisher's exact test; Pearson's χ^2 test)
	n	%	n	%	
Gastrointestinal disorders					1.000
Dyspepsia	2	1.26	1	0.63	
Nausea	1	0.63	0	0.00	
Infections and infestations					1.000
Upper respiratory tract infection	1	0.63	2	1.26	
Respiratory tract infection	0	0.00	1	0.63	
Viral pneumonia	0	0.00	1	0.63	
Investigations					—
Increase in blood pressure	0	0.00	2	1.26	
Increased alanine aminotransferase level	0	0.00	3	1.89	
Increased aspartate aminotransferase level	0	0.00	2	1.26	
Increase in blood creatinine level	0	0.00	1	0.63	
Increase in blood urea nitrogen level	0	0.00	1	0.63	
Respiratory, thoracic and mediastinal disorders					—
Nasal itching	2	1.26	0	0.00	
Throat irritation	4	2.51	0	0.00	
Sneeze	1	0.63	0	0.00	
Skin and subcutaneous tissue disorders					—
Rash	1	0.63	0	0.00	
Musculoskeletal and connective tissue disorders					1.000
Arthralgia	2	1.26	1	0.63	
Pain in extremity	0	0.00	1	0.63	
Back pain	1	0.63	0	0.00	
Joint stiffness	0	0.00	1	0.63	
Nervous system disorders					0.400
Dizziness	1	0.63	2	1.26	
Dysgeusia	2	1.26	0	0.00	
Balance disorder	0	0.00	1	0.63	
Renal and urinary disorders					0.714[a]
Hematuria	0	0.00	2	1.26	
Hyperoxaluria	0	0.00	1	0.63	
Glycosuria	0	0.00	1	0.63	
Leukocyturia	1	0.63	0	0.00	
Kidney pain	0	0.00	1	0.63	
Proteinuria	0	0.00	1	0.63	
Cardiac disorders					—
Right His bundle branch block	0	0.00	1	0.63	
Heart pounding	0	0.00	1	0.63	
Tachycardia	0	0.00	1	0.63	
Hyperemia	0	0.00	1	0.63	
General disorders and administration site conditions					—
Fever sensation	0	0.00	1	0.63	
Mental disorders					—
Panic attack	0	0.00	1	0.63	

Note. [a] — The values were calculated as the number of patients with AE development and their proportion in the safety population (n=159) for each of the groups.

of therapy (completion of parenteral administration). Statistically significant differences between the groups on the Digit symbol substitution test, SF-36 questionnaire (mental component of health) and MFI-20 scale have been revealed from the 4th week of treatment (parenteral phase and one month of oral therapy). Statistically significant differences between the groups on the Vane questionnaire were noted at the end of long-term sequential therapy.

Positive dynamics in presence of long-term sequential therapy with Mexidol and Mexidol FORTE 250 medications had an increasing character in assessment on all indicated scales, tests and questionnaires. Consequently, treatment with Mexidol led to significant regression of the severity of such important manifestations of CBI as cognitive, emotional, autonomic and motor disorders. Simultaneous significant regression of all major clinical manifestations of CBI is an important argument in favor of the fact that therapy with Mexidol has an effect on the pathogenetic basis of chronic cerebral vascular lesions, not limited to symptomatic improvement.

The results of statistical analysis of the incidence of AEs, indicators of laboratory assessment and physical examination have shown the absence of significant differences between the compared groups in terms of the main safety parameters, which indicates good tolerability of sequential therapy with Mexidol and Mexidol FORTE 250 and a safety profile comparable to placebo, including in patients who received baseline therapy (antiaggregants, antihypertensive, hypolipidemic agents).

Thus, clinical efficacy, safety of use and good tolerability allow us to recommend the use of Mexidol in everyday practice for the treatment of patients with CBI as a means of pathogenetic therapy of cognitive, emotional, autonomic and motor disorders.

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