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Results of a Randomized, Double-Blind, Multicenter, Placebo-Controlled, Parallel-Group Study of the Efficacy and Safety of Mexidol in Prolonged Sequential Therapy of Patients in the Acute and Early Recovery Stages of Hemispheric Stroke (the EPICA study)

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Objectives. To assess the efficacy and safety of prolonged sequential therapy with Mexidol in patients with hemispheric ischemic stroke (IS) in the acute and early recovery phases. **Materials and methods.** A randomized, double-blind, multicenter, placebo-controlled, parallel-group study included 151 patients (62 men and 89 women) was performed in which 150 patients (62 men and 88 women) aged 40–79 years were randomized. Simple randomization was used to define two groups: patients of group 1 received Mexidol therapy at a dose of 500 mg/day by intravenous infusion for 10 days followed by oral doses of 1 tablet (125 mg) three times a day for eight weeks. Patients of group 2 received placebo by the same protocol. The duration of involvement in the trial was 67–71 days. **Results.** At the end of treatment, mean scores on the modified Rankin scale (mRS) were lower in group 1 than group 2 ($p = 0.04$). Decreases in mean mRS scores (at visits 1–5) were more marked in group 1 ($p = 0.023$). The proportion of patients achieving recovery corresponding to 0–2 points on the mRS (at visit 5) was significantly greater in group 1 ($p = 0.039$). Testing on the National Institutes of Health Stroke Scale at visit 5 gave a significantly lower score in group 1 ($p = 0.035$). Decreases in scores on the National Institutes of Health Stroke Scale at the end of treatment relative to the baseline level in patients with diabetes mellitus were more marked in group 1 ($p = 0.038$). In group 1, the total population and the subpopulation of patients with diabetes mellitus showed more marked improvements in quality of life, which was apparent by visit 2. The proportion of patients without difficulty mobilizing was significantly greater in group 1 ($p = 0.022$). There were no significant differences in the frequencies of adverse events in patients of the two groups. **Conclusions.** Use of Mexidol in the acute and early recovery phases of IS is recommended.

Keywords: acute cerebrovascular accident, Mexidol, ethylmethylhydroxypyridine succinate, efficacy and safety, ischemic stroke, acute phase, early recovery phase, EPICA.

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The treatment of ischemic stroke (IS) currently involves several stages (emergency care, in-patient treatment, rehabilitation), and includes reperfusion, neuroprotection, prevention of reocclusion, and treatment of complications, and depends on the severity of disease. The relevance of the problem of IS comes from its significant incidence and the high levels of resultant disability and death [1].

One of the most complex problems is that of selecting effective and safe neuroprotective therapy, and this is among the main directions of the treatment of patients with IS. The main aim of treatment is the protect neurons from the harmful actions of the ischemic cascade at the cellular and molecular levels. Accumulated experience shows that the zone of irreversible changes in the brain in IS expands gradually, with development of the ischemic cascade to one extent or another [2]. Timely intervention using neuroprotective agents can prevent or inhibit the mechanisms leading to neuron death in areas of ischemic tissue. Primary neuroprotection is directed to interrupting the rapid mechanisms of the glutamate-calcium cascade with the aim of correcting the imbalance between excitatory and inhibitory neurotransmitters. Secondary neuroprotection is directed to interrupting the delayed mechanisms of cell death and includes the use of trophic factors, antioxidants, neuropeptides, etc. Neuroprotective defense of ischemically damaged nerve tissue is more effective in the early phases of the development of IS [3].

Therapeutic substances improving neuron metabolism include ethylmethylhydroxypyridine succinate (Mexidol), which has been actively used for many years in neurology for the treatment of patients with acute and chronic cerebrovascular diseases. Experimental studies have demonstrated that Mexidol influences the development of excitotoxicity in vitro. Mexidol suppresses the development of glutamate-induced neurotoxicity and ascorbate-dependent (non-enzymatic) and $NADPH_2$-dependent (enzymatic) iron-induced lipid peroxidation, and has the ability to bind the superoxide anion radical and increase the activity of Se-dependent glutathione peroxidase [4]. These effects underlie its antioxidant and antihypoxant actions [5]. The results of a chemoreactome analysis of the Mexidol molecule showed that the main targets of its pharmacological action were acetylcholine and $GABA_A$ receptors, the enzyme COX-2, 5-lipoxygenase (5-LPO), and PPAR receptors [6].

There is extensive experience of the clinical use of Mexidol in acute and chronic cerebral ischemia. A randomized double-blind, placebo-controlled study of the efficacy and safety of Mexidol in the complex treatment of the acute phase of IS found significantly faster regression of neurological impairments on the National Institutes of Health Stroke Scale by day 14 of illness as compared with the placebo group ($p < 0.05$), along with significant functional recovery (changes in the Bartel index (BI)) on day 21 ($p < 0.05$) in the first 6 h of illness in the study patients [7].

Analysis of the efficacy and safety of Mexidol and its effects on the dynamics of the neurological manifestations of illness, emotional status, and quality of life in patients with chronic cerebral ischemia showed that by the end of the trial, patients of the study group experienced significant reductions in the severity of motor impairments and normalization of quality of life (SF-36 scale), along with significant improvements in cognitive functions. The high efficacy and safety of treating patients with chronic cerebral ischemia with Mexidol was confirmed [8]. Thrombolytic therapy (TLT) combined with Mexidol led to significantly faster reductions in the severity of neurological deficit and somatic complications. TLT combined with Mexidol created the conditions not only for recovery of neurological functions, but also for preventing harmful secondary reactions from causing brain damage [9].

Inclusion of Mexidol into complex recuperative treatment significantly improved rehabilitation results, promoting restoration of neurological functions and increasing the level of adaptation to daily life [10].

Positive effects were demonstrated for Mexidol in patients in the hyperacute and acute phases of IS. On the background of i.v. and i.m. administration, compete regression of general cerebral symptoms was obtained, with more complete regression of focal deficit, which defined the value of using Mexidol in complex therapy [11]. One of the most helpful effects of Mexidol when included in complex therapy was a significant reduction in the hour-by-hour death rate in the cute period of IS, along with the tendency to a general slowing of lethality [12, 13]. Sequential use of injection and tablet forms of Mexidol promoted reductions in neurological symptomatology in patients with IS in the vertebrobasilar system [14].

Thus, the results of previous studies provide evidence of the efficacy of Mexidol in the treatment of patients with IS; there is a need for assessing the efficacy and safety of this drug in conditions of treatment using prolonged courses.

The aim of the present work was to assess the efficacy and safety of prolonged sequential therapy with Mexidol (solution for i.v. and i.m. administration, tablets) in patients with hemispheric IS in the acute and early recovery stages.

Materials and Methods. A multicenter, prospective, randomized, double-blind, placebo-controlled, parallel-group study was conducted.

Inclusion criteria: primary hemispheric IS confirmed by CT/MRI; age 40–80 years; ability to understand the purpose of the study and comply with the protocol requirements; hospitalization no more than 72 h from the onset of IS; scores on the modified Rankin scale at enrolment 3 points or more; scores on the National Institutes of Health Stroke Scale 5–20 points; scores on the Beck Depression Scale of less than 19 points; informed consent form signed and dated by patient (or an independent witness who was not a member of the research team and not a direct subordinate of the principal investigator if the patient was physically unable to sign); negative pregnancy test in women of childbearing age; agreement of female patients to use ap-

TABLE 1. Protocol and Visit Contents

Parameter	Visits, timing (days into study)						
	Visit 1 Day 1	Visit 2 Day 11	Visit 3 Last day of in-patient phase	Active telephone call	Visit 4 Day 36–42	Active telephone call	Visit 5 Day 67–71
Neurological examination	×	×	×		×		×
Assessment of general status, clinical symptoms	×	×	×		×		×
Anthropometric measures	×						×
Informed consent signed by patient	×						
Inclusion of patient in study	×						
Pregnancy test	×						
Randomization	×						
Collection of information on concomitant treatment	×	×	×	×	×	×	×
ECG	×	×	×		×		×
Clinical blood tests	×	×	×		×		×
General urine tests	×		×		×		×
Biochemical blood tests	×	×	×		×		×
Issue of medication	×	×			×		
Assessment of quantity of drug taken and/or assessment of compliance		×	×	×	×	×	×
Recording of adverse events	×	×	×	×	×	×	×
Provision of individual medical records by patient	×	×	×	×	×	×	×
Modified Rankin scale	×	×	×		×		×
National Institutes of Health Stroke Scale	×	×	×		×		×
Beck Depression Scale	×	×				×	×
Screening questionnaire for identifying cognitive impairments	×	×				×	×
Frontal Assessment Battery	×	×				×	×
Bartel index	×	×	×		×		×
Quality of life questionnaire evaluation (EQ-5D)	×	×					×

propriate methods of contraception and/or readiness of partners of male patients to use contraception or abstention from sex during the study period.

Non-inclusion criteria. Absence of hemispheric IS confirmed by CT/MRI; age less than 40 or more than 80 years; scores on the National Institutes of Health Stroke Scale less than 5 or greater than 20 points; hemorrhagic stroke; hemorrhagic infarct; recurrent IS; Parkinson's disease; epilepsy; demyelinating disease of the nervous system; inherited degenerative diseases of the CNS; history of infectious diseases of the CNS; traumatic brain injury with severe neurological symptomatology and cognitive impairment; unstable angina; myocardial infarction within last three months; chronic heart failure functional class IV; atrioventricular block stage II–III; systemic connective tissue diseases; chronic obstructive pulmonary disease stage III–IV; acute surgical pathology; uncompensated heart, liver, or kidney disease; acute/chronic liver/kidney failure; history of oncological disease; immunodepressed state; tuberculosis; alcohol or drug addiction; mental illness; history of any state felt by the investigating physician to prevent inclusion in the study; acute infectious diseases within the

TABLE 2. Initial Demographic and Clinical Laboratory Characteristics of Patients ($M \pm SD$)

Characteristic	All patients (n = 150)		Diabetes mellitus (n = 31)		TLT (n = 24)	
	Group 1 (n = 75)	Group 2 (n = 75)	Group 1 (n = 15)	Group 2 (n = 16)	Group 1 (n = 12)	Group 2 (n = 12)
Gender, %						
men	41.3	41.3	46.7	31.3	41.7	41.7
women	58.7	58.7	53.3	68.8	58.3	58.3
Age, years	63.9 ± 10.3	61.5 ± 8.7	66.1 ± 9.4	64.1 ± 8.7	63.5 ± 14.9	61 ± 11.6
Height, cm	168.6 ± 8.7	168.4 ± 8.6	167.2 ± 7.6	169.1 ± 8.8	170.8 ± 7.6	167.3 ± 7.6
SBP, mmHg	138.8 ± 14.3	138.7 ± 14.8	143.3 ± 18.7	144.6 ± 17.4	140.6 ± 18.6	142.1 ± 19.2
DBP, mmHg	83.6 ± 7.8	81.6 ± 8.0	83.6 ± 7.4	85.2 ± 8.2	84.7 ± 10.6	83.2 ± 10.7
Glucose, mM	6.6 ± 2.4	6.5 ± 2.7	10.0 ± 3.4	9.2 ± 4.9	6.3 ± 1.8	5.5 ± 0.9
Cholesterol, mM	5.8 ± 1.2	5.4 ± 1.2	6.6 ± 1.5	5.5 ± 1.3	5.5 ± 1.0	5.4 ± 1.2

SBP – systolic blood pressure; DBP – diastolic blood pressure. Here and Tables 3–7: M – arithmetic mean; SD – standard deviation; TLT – thrombolytic therapy.

TABLE 3. Initial Clinical Characteristics of Study Patients ($M \pm SD$)

Characteristic	All patients (n = 150)		Diabetes mellitus (n = 31)		TLT (n = 24)	
	Group 1 (n = 75)	Group 2 (n = 75)	Group 1 (n = 15)	Group 2 (n = 16)	Group 1 (n = 12)	Group 2 (n = 12)
Modified Rankin scale, points	3.5 ± 0.5	3.4 ± 0.5	3.5 ± 0.5	3.6 ± 0.6	3.3 ± 0.5	3.7 ± 0.5
National Institutes of Health Stroke Scale, points	6.9 ± 1.8	7.3 ± 2.4	7.2 ± 2.3	6.8 ± 2.0	6.0 ± 1.4	6.7 ± 2.2
Beck Depression Scale, points	8.2 ± 4.4	9.1 ± 4.6	9.1 ± 4.6	9.2 ± 4.5	7.6 ± 3.1	7.9 ± 3.3
Cognitive-affective subscale of Beck Depression Scale, points	4.1 ± 2.7	4.5 ± 2.8	4.6 ± 2.7	4.3 ± 2.6	3.3 ± 1.2	3.8 ± 1.9
Somatic Signs Subscale of Beck Depression Scale, points	4.2 ± 2.4	4.6 ± 2.4	4.5 ± 2.3	4.9 ± 2.4	4.3 ± 2.5	4.1 ± 2.2
Bartel index, points	54.5 ± 18.7	53.7 ± 21.1	48.3 ± 20.2	50.0 ± 21.4	48.3 ± 13.5	47.9 ± 16.2
Frontal Assessment Battery:	n = 75	n = 74				
normal function	26	28	4	6	6	5
moderate dysfunction	33	28	8	6	4	5
severe dysfunction	16	18	3	4	2	2
Screening questionnaire for cognitive impairments:						
no severe impairments	61	64	13	13	11	11
severe impairments	14	10	2	3	1	1

four weeks prior to the study; reports of lactose intolerance or congenital galactose intolerance; Lapp lactase deficit, or glucose-galactose malabsorption syndrome; pregnancy or breastfeeding; mental, physical, or other reasons preventing adequate assessment of status and correct compliance with the conditions of the study protocol; patients who are staff members of the study center or sponsor company or members of their families; participation in clinical drug trials during the three months period to the start of the study; any state or circumstance which the investigator believes will hinder participation in the study; individual intolerance of Mexidol or formulations containing succinic acid salts

or vitamin B_6; contraindications to the use of Mexidol; lack of informed consent form independently signed and dated by the patient (or another independent witness if the patient was physically unable to sign).

Exclusion criteria: first detection of the states or illnesses described in the non-inclusion criteria; first signs of hypersensitivity to ethylmethylhydroxypyridine succinate; noncompliance by the patient with the study protocol; desire of patient to leave the study/rescinding of informed consent by patient; any state of the patient which the investigating physician believed required the patient to leave the study; adverse events and serious adverse events whose development was felt by the investigator to make continued participation in the study dangerous for the patient's health or wellbeing; lack of follow-up observations of the measurements specified in the study protocol; detection of use by the patient of drugs not approved for the study; administrative reasons, including protocol violations which could affect the study results.

Study participants were distributed to two groups by simple randomization. Patients of group 1 received Mexidol at a dose of 500 mg/kg by i.v. infusion for 10 days with subsequent use of 125-mg tablets, one tablet three times a day, for eight weeks. Patients of group 2 received placebo by the same protocol. The duration of courses of treatment with Mexidol was 66 (10 + 56) days, and the total duration of patients' involvement in the trial was at least 67 days and no more than 71 days. The schedule and content of visits is given in Table 1.

All patients involved in the study received complete treatment for IS as defined by the standard indications for medical assistance and clinical recommendations. Prescription and use of the following drugs and/or biologically active supplements were not approved: drugs containing succinic acid and its salts (Reamberin, Remaxol, Cytoflavin) or vitamin B_6 and/or its derivatives; antioxidants and antihypoxants; nootropic agents.

The study included 151 patients (62 men and 89 women) of whom 150 patients (62 men and 88 women) aged 40–79 years were randomized; one patient was lost to the study at the screening stage. of the 150 patients suitable for administration, 141 completed the study and nine terminated prematurely. The efficacy analysis included 124 patients who completed the study in compliance with the protocol. In addition, efficacy analysis was performed in subpopulations of patients: a group of patients with diabetes mellitus included 24 patients (11 of group 1 and 13 of group 2), a group of patients receiving TLT therapy consisted of 22 patients (11 from group 1 and 11 from group 2); the safety analysis included data from 150 patients (62 men and 88 women) who underwent clinical and laboratory instrumented investigations. The groups were comparable in terms of demographic, clinical, and laboratory data (Tables 2 and 3).

The primary criterion for assessment of efficacy (the primary endpoint) was the test result on the modified Rankin scale at the end of treatment courses. Secondary criteria for efficacy assessments (secondary endpoints) were test results at the end of treatment courses: the National Institutes of Health Stroke Scale, the Bartel index, the screening questionnaire for defining cognitive impairments, the Frontal Assessment Battery, the Beck Depression Scale, and a quality of life assessment questionnaire (EQ-5D).

Treatment safety was evaluated using physical examination data, general clinical assessment, blood biochemistry, the coagulogram, general urine tests, the ECG, and the frequency and severity of adverse events (AE).

Statistical processing was run in the statistics programming language *R*. Test results are described using the arithmetic mean (*M*), standard deviation (*SD*), median (*Me*), quartiles, minima (Min), maxima (Max), and the coefficient of variation. Changes in each group were assessed using the Friedman test. Comparison of values between groups at each visit was performed using the nonparametric Mann and Whitney U test, and frequencies were compared using Fisher's exact test or a frequencies equality test.

For quantitative values, changes in points scores at the end of treatment courses relative to baseline levels were calculated, along with *M* and *SD* and 95% confidence limits for differences in means. Between-group comparisons were run using the Mann–Whitney test. Results were tested on the EQ-5D scale in terms of frequencies and percentages.

Frequencies between groups were compared at each visit using Fisher's exact test or Person's χ^2 test; assessment of changes in test results using categorial scales at the moment of completing treatment courses relative to baseline was with the McNemar test or the Stuart–Maxwell test.

Analysis of safety parameters for interval (quantitative) data for each visit was run by computing *M*, *SD*, *Me*, quartiles, min, max, the coefficient of variation, and the 95% confidence interval (for data with normal distributions). After verifying interval data for normal distributions (using the Shapiro–Wilks test), assessment of changes in quantitative data was performed using the Friedman test or unifactorial analysis of variance (ANOVA). When statistically significant differences in dynamics were found in groups, pairwise comparisons of data between visits in this group were made using the nonparametric Wilcoxon *T* test for dependent sets or Student's *t* test for linked sets.

Results and Discussion. ***Primary efficacy criteria.*** Both groups showed improvements, which were apparent as reductions in mean values on assessments using the modified Rankin scale. A statistically significant difference between groups ($p = 0.04$) was seen at visit 5: 1.1 ± 0.8 points in group 1 and 1.5 ± 1.0 points in group 2. Assessment of changes in scores on the modified Rankin scale at the end of treatment relative to baseline (visits 1–5) identified significant differences ($p = 0.023$) between groups: 2.3 ± 0.7 in group 1 and 2.0 ± 0.8 points in group 2. Group 1 showed a more marked decrease in the arithmetic mean score on the modified Rankin scale compared with baseline.

TABLE 4. Results of Testing on the National Institutes of Health Stroke Scale

Parameter	Visit 1 (day 1)	Visit 2 (day 11)	Visit 4 (day 36–42)	Visit 5 (day 67–71)	p^{**}	p^{***}
Group 1 (n = 61)						
$M \pm SD$	6.9 ± 1.8	3.7 ± 2.3	2.2 ± 1.5	1.7 ± 1.4	<0.001	<0.001
Me	6	3	2	1		
lower–upper quartile	6–8	2–5	1–3	1–3		
Group 2 (n = 63)						
$M \pm SD$	7.2 ± 2.2	4.0 ± 2.1	2.7 ± 1.7	2.2 ± 1.4	<0.001	<0.001
Me	7	4	3	2		
lower–upper quartile	5–8	3–5	1–4	1–3		
p^{*}	0.589	0.302	0.126	0.035		

$^{*}p$ – comparison of values between groups (Mann–Whitney U test); p^{**} – assessment of dynamics (Friedman test); p^{***} – comparison of values at the end of treatment (visit 5) relative to baseline value (visit 1) (Wilcoxon T test). Here and in Tables 6 and 7: *Me* – median.

TABLE 5. Results of Testing on the Beck Depression Scale

Group	Absence of symptoms of depression, n (%)				p^{**}
	Visit 1	Visit 2	Visit 4	Visit 5	
All patients (n = 124)					
Group 1 (n = 61)	42 (68.9)	51 (83.6)	55 (90.2)	57 (93.4)	<0.001
Group 2 (n = 63)	36 (57.1)	43 (68.3)	51 (81)	54 (85.7)	<0.001
p^{*}	0.446	0.105	0.247	0.241	
Patients with TLT (n = 11)					
Group 1 (n = 11)	8 (72.7)	10 (90.9)	11 (100)	11 (100)	0.019
Group 2 (n = 1)	8 (72.7)	7 (63.6)	8 (72.7)	9 (81.8)	0.544
p^{*}	1.00	0.311	0.214	0.476	

p^{*} – comparison of frequencies between groups; p^{**} – assessment of dynamics of frequencies (χ^2 test for linear trend).

It should also be noted that there was a significant difference in the proportions of patients achieving recovery to 0–2 points on this scale at the end of treatment courses (visit 5): this occurred in 59 patients in group 1 (96.7%) and in 53 patients in the placebo group (84.1%) (p = 0.039).

Secondary efficacy criteria. Testing on the National Institutes of Health Stroke Scale identified improvements in both groups. At visit 5, there was a statistically significant difference between total scores in the treatment groups; the mean value in group 1 was lower, at 1.7 ± 1.4 points, than in group 2, at 2.2 ± 1.4 points (p = 0.035) (Table 4). Assessment of changes in total scores on the National Institutes of Health Stroke Scale at the end of treatment relative to baseline (visits 1–5) revealed a statistically significant difference between groups of patients with diabetes mellitus: 5.4 ± 2.3 points in group 1 (n = 11) and 4.0 ± 1.4 points in group 2 (p = 0.038).

Testing using the Bartel index, the Frontal Assessment Battery, and the screening questionnaire for assessing cognitive impairments in patients showed improvements, with no statistically significant differences between treatment groups.

On assessment of status on the Beck Depression Scale, both groups showed significant increases in the numbers of patients without symptoms of depression from visit 1 to visit 5 ($p < 0.001$), and an analogous relationship was found in patients undergoing TLT in group 1 (p = 0.019) (Table 5).

Assessment of status on the cognitive-affective subscale of the Beck Depression Scale showed a statistically significant difference between baseline levels and values at the end of treatment in both groups ($p < 0.001$). In the subpopulation of patients with diabetes mellitus, there was a statistically significant difference (p = 0.014) between baseline and final values in group 1 but not in group 2 (Table 6).

TABLE 6. Results of Testing on the Beck Depression Scale (total points on the cognitive-affective subscale) in Patients with Diabetes Mellitus

Parameter	Visit				*p***	*p****
	1	2	4	5		
Group 1, *n* = 11					0.002	0.014
M ± *SD*	4.2 ± 2.8	1.8 ± 2.6	1.8 ± 1.3	1.3 ± 1.5		
Me	3	1	1	1		
lower–upper quartile	2.5–6	0.5–2	1–2.5	0–2.5		
Group 2, *n* = 13					0.225	0.064
M ± *SD*	4.5 ± 2.7	3.5 ± 2.0	3.9 ± 2.1	2.7 ± 1.7		
Me	4	4	4	2		
lower–upper quartile	2–6	1–5	2–6	2–4		
*p**	0.77	0.028	0.013	0.041		

*p** – comparison of values between groups (Mann–Whitney test); *p*** – assessment of dynamics (Friedman test); *p**** – comparison of values at the end of treatment (visit 5) relative to baseline (visit 1) (Wilcoxon T test).

TABLE 7. Results of Testing on the EQ-5D Quality of Life Questionnaire

Parameter	Visit			*p***	*p****
	1	2	5		
All patients (n = 124)					
Group 1, *n* = 61				<0.001	<0.001
M ± *SD*	47.6 ± 17.4	71.6 ± 15.8	83.8 ± 15.5		
Me	50	70	90		
lower–upper quartile	40–60	60–90	80–95		
Group 2, *n* = 63				<0.001	<0.001
M ± *SD*	43.8 ± 20.3	64.4 ± 17.6	78.2 ± 17.5		
Me	40	63	80		
lower–upper quartile	30–50	50–77.5	70–90		
*p**	0.13	0.019	0.044		
Patients with diabetes mellitus (n = 24)					
Group 1, *n* = 11				<0.001	0.004
M ± *SD*	45.5 ± 18	75.8 ± 14.3	89 ± 9.4		
Me	50	74	90		
lower–upper quartile	27.5–55	70–85	80–99		
Group 2, *n* = 13				0.001	0.005
M ± *SD*	37.7 ± 14	60.2 ± 18.3	72.3 ± 21.8		
Me	35	60	80		
lower–upper quartile	30–40	50–75	65–85		
*p**	0.305	0.055	0.043		

*p** – comparison of values between groups (Mann–Whitney *U* test); *p*** – assessment of dynamics (Friedman test); *p**** – comparison of values at the end of treatment (visit 5) relative to baseline (visit 1) (Wilcoxon T test).

TABLE 8. Results of Testing on the EQ-5D Questionnaire (assessment on "mobility" domain of the health subscale, points)

Assessment on subscales of EQ-5D questionnaire	Frequency, *n* (%)		
	Visit 1	Visit 2	Visit 5
Group 1 ($n = 61$)			
I have no problem with mobility in space	8 (13.1)	34 (55.7)	53 (86.9)
I have some problems with mobility in space	42 (68.9)	27 (44.3)	8 (13.1)
I am confined to bed	11 (18)	0	0
Group 2 ($n = 63$)			
I have no problem with mobility in space	4 (6.3)	20 (31.7)	43 (68.3)
I have some problems with mobility in space	42 (66.7)	42 (66.7)	19 (30.2)
I am confined to bed	17 (27)	1 (1.6)	1 (1.6)
Test (Fisher's exact test, Pearson's χ^2 test, p)	0.297	0.011	0.022

p – comparison of values between groups. Assessment of changes in frequency (χ^2 test for confirmation of linear trend), $p < 0.001$.

Statistically significant differences between groups were seen at visits 2, 4, and 5.

On testing using the EQ-5D quality of life questionnaire, significant changes ($p < 0.001$) were seen during the study, with statistically significant differences between values at visits 1 and 5 in both groups ($p < 0.001$). Statistically significant differences between groups were found at visits 2 and 5 (Table 7). Analogous results were obtained in the subpopulation of patients with diabetes mellitus, in whom there was a significant improvement during the study, with a significant difference between values at visits 1 and 5 ($p = 0.004$ for group 1 and $p = 0.005$ for group 2). A significant difference between groups was seen at visit 5 (see Table 7).

Separate analysis of functions using the EQ-5D questionnaire ("mobility" scale in the health domain) identified a significant ($p < 0.001$) linear relationship in both groups, with increases in the numbers of patients without mobility problems, along with a statistically significant difference between groups at visits 2 ($p = 0.011$) and 5 ($p = 0.022$) (Table 8). A total of 53 patients of group 1 (86.9%) noted that they had no mobility problems, while 48 (78.7%) noted the absence of difficulties with self-care, and 43 (70.5%) had no problems with the activities of daily living (work, studying, household chores, family obligations, leisure activities); 52 patients (85.2%) felt no pain or discomfort; 54 (88.5%) did not experience anxiety or depression.

Safety assessment. The tolerance of Mexidol and placebo was evaluated as satisfactory; 41 adverse events (AE) were recorded in 32 patients. A total of 37 cases of AE were noted in 28 patients (Table 9), along with four of serious AE (SAE).

For most recorded AE, the link with the study agents was absent; in three cases it was assessed as possible. These abnormalities were random in nature and could develop on the background of the main and concomitant diseases. Four SAE were recorded in four patients: one in group 1 and three in group 2. In group 2, SAE included recurrent severe IS, severe hemorrhagic stroke, and acute cholecystitis. A case of severe recurrent stroke occurred in a group 1 patient. In all cases, there was no connection with treatment. All four patients developing SAE were excluded from the trial and the study therapy was withdrawn. There were no lethal outcomes.

There were no significant differences in the frequencies of AE/SAE in patients of both groups. The data obtained here provide evidence that Mexidol (solution for i.v. and i.m. use and film-coated tablets) and placebo are comparable in patients in the acute and early recovery phases of hemispheric IS.

Conclusions. The efficacy and safety of prolonged sequential treatment with Mexidol as compared with placebo were evaluated in a clinical trial in patients in the acute and early recovery phases of hemispheric IS. During Mexidol treatment, there were significant decreases in symptoms and functional impairments. During Mexidol treatment, there were significantly greater improvements in life activity measured on the modified Rankin scale, as compared with placebo. At the end of treatment, the level of life activity was significantly greater in the Mexidol treatment group. Recovery to 0–2 points on the modified Rankin scale was noted in 96.7% of patients in the Mexidol group and 84.1% in the placebo group ($p = 0.039$).

At the end of treatment, neurological deficit significantly lower in the Mexidol treatment group than the placebo group on testing using the National Institutes of Health Stroke Scale. Positive actions of Mexidol treatment were obtained in patients with concomitant diabetes mellitus.

Mexidol treatment promoted significant improvements in quality of life, starting from visit 2. The vast majority of patients in the Mexidol treatment group noted that they had

TABLE 9. Adverse Events not Meeting the Seriousness Criterion

AE	Group 1 (n = 75)		Group 2 (n = 75)	
	n	%	n	%
Metabolism:				
exacerbation of gout	1	1.33	2	2.67
dyslipidemia	1	1.33	0	0
elevated liver enzymes	1	1.33	0	0
type 2 diabetes mellitus	0	0	1	1.33
CBS:				
episodes of reduced consciousness	1	1.33	0	0
headache	1	1.33	2	2.67
intermittent vertigo	0	0	1	1.33
Musculoskeletal system				
back pain	1	1.33	4	5.33
knee joint pain	1	1.33	0	0
Cardiovascular system:				
elevated arterial pressure	1	1.33	0	0
persistent form of atrial fibrillation	1	1.33	0	0
hypertensive crisis	1	1.33	1	1.33
sinus bradycardia	0	0	1	1.33
Gastrointestinal tract and digestive system:				
erythematous gastropathy	1	1.33	0	0
Kidneys and urinary system:				
urinary tract infection	1	1.33	0	0
exacerbation of chronic cystitis	1	1.33	0	0
exacerbation of chronic pyelonephritis	0	0	1	1.33
Visual organs:				
cataract	1	1.33	0	0
bilateral retinal angiopathy	1	1.33	0	0
Hearing and balance organs:				
sensorineural deafness	0	0	1	1.33
Other AE:				
angiolipoma	1	1.33	0	0
allergic rhinitis	1	1.33	0	0
abscess of anterior abdominal wall	1	1.33	0	0
closed fracture of ribs 8–9 on the left	1	1.33	0	0
injury to right half of chest wall and right lumbar area	1	1.33	0	0
acute respiratory viral infection	1	1.33	1	1.33
nosebleed	0	0	1	1.33

p – mean value between groups (Fisher's exact test) > 0.05.

no difficulties with locomotion, self-care, or performance of chores, and that they had no pain or discomfort, anxiety, or depression.

In the subpopulation of patients with diabetes mellitus, quality of life in the Mexidol treatment group was significantly better at the end of treatment.

The safety of prolonged sequential treatment with Mexidol was demonstrated in patients with IS in the acute and early recovery phases. The study results provided evidence that Mexidol used as sequential therapy has a favorable tolerability and safety profile. Mexidol can be recommended as a component of the treatment of patients in the acute and early recovery phases of IS.

The authors have no conflicts of interests.

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