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Research Article

# COMPARATIVE ANALYSIS OF THE CLINICAL EFFICACY OF COMBINED NEUROPROTECTION IN PATIENTS WITH ISCHEMIC STROKE ON THE BACKGROUND OF COVID-19

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## ABSTRACT

This article discusses the comparative analysis of the clinical efficacy of combined neuroprotection in patients with ischemic stroke on the background of COVID-19. To study the effect of the developed measures for drug and non-drug therapy, which included exercises (exercise therapy), patients were observed for the first 3 months of treatment. The second subgroup MG-2 received standard therapy with observation at the same time. Exercise therapy was developed in collaboration with instructors and rehabilitation specialists.

## KEYWORDS

Comparative analysis, combined neuroprotection, ischemic stroke, background of COVID-19, non-drug therapy, exercise therapy, treatment, standard therapy.

## INTRODUCTION

In most modern medical scientific research, the rehabilitation treatment of post-stroke patients is characterized by the introduction of combined neuroprotection (3,5,6,8,9). The main focus of rehabilitation treatment with combined neuroprotection is on the ability of the nervous tissue

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to structural and functional restructuring and reorganization (1). Such a combination are nootropic drugs with neurotransmitter properties, and drugs of neuropeptide origin. The most famous of them are "Citicoline" and "Edaravone" (4,4,7). In our opinion, the combination of these drugs is interesting and relevant, since the multidirectional properties of these drugs can significantly increase the effectiveness of the rehabilitation treatment of patients with ischemic stroke.

Purpose of the study. To analyze the clinical efficacy of combined neuroprotection in patients with ischemic stroke on the background of COVID-19.

Material and research methods. Patients with AT and CE subtypes of stroke were selected for the study at this stage due to the presence of pronounced neurological symptoms in them. When prescribing drug therapy, the MG and CG groups were divided into subgroups 1 and 2. MG-1 included 48 patients from the study MG - 29 (61.5%) men and 19 (39.6%) women. MG-2 included 30 patients - 19 (63.3%) men and 11 (36.7%) women (v.6.1) CG-1 included 23 patients - 13 (56.5%) men and 10 (43 .5% of women, CG-2 included 21 people - 10 men (47.6%) and 11 (52.4%) women (v.1).

**Table 1.**

**Subgroups of MG and CG depending on gender**

| | subgroups | total | | men | | women | |
|---|---|---|---|---|---|---|---|
| | | abc | % | abc | % | abc | % |
| 78 | **MG -1** | 48 | 61,5% | 27 | 56,3% | 21 | 43,8% |
| 78 | **MG-2** | 30 | 38,5% | 19 | 63,3% | 11 | 36,7% |
| 122 | **total** | **78** | **63,9%** | **46** | **59,0%** | **32** | **41,0%** |
| 44 | **CG -1** | 23 | 52,3% | 13 | 56,5% | 10 | 43,5% |
| 44 | **CG -2** | 21 | 47,7% | 10 | 47,6% | 11 | 52,4% |
| 122 | **total** | **44** | **36,1%** | **23** | **52,3%** | **21** | **47,7%** |
| 122 | *total* | *122* | *100,0%* | *69* | *56,6%* | *53* | *43,4%* |

Patients MG-2 and CG-2 received conventional therapy (basic and differentiated). In addition to conventional therapy, the following neuroprotective drugs were added to patients MG-1 and CG-1:

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- Citicoline (Ceraxon, Takeda, Japan) was administered at a dose of 1000 mg/day intravenously for 10 days;

- Edaravone (Xavron, Yuria-Pharm, Ukraine) in the form of 30 mg of the drug (1 ampoule) twice a day, in the morning and in the evening, by intravenous infusion for 30 minutes, 10 days.

To study the effect of the developed measures for drug and non-drug therapy, which included exercises (exercise therapy), patients were observed for the first 3 months of treatment. The second subgroup MG-2 received standard therapy with observation at the same time. Exercise therapy was developed in collaboration with instructors and rehabilitation specialists.

To objectify the severity of the condition, the severity of focal neurological deficit and assess the dynamics of clinical parameters, the National Institutes of Health Stroke Score Scale (NIHSS) was used, the degree of functional recovery was assessed using the modified Rankin scale, and the assessment of cognitive status was measured using the Montreal Cognitive Assessment Scale (MoCA). The data obtained indicate the effectiveness of the combined neuroprotection of "Citicoline" and "Edaravone" in the acute period of ischemic stroke in comparison with conventional therapy.

The survey was carried out by the method of continuous research, the results of observations were used. Statistical processing of clinical and instrumental materials in accordance with the recommendations for processing the results of biomedical research at a significance level of $p<0.05$ was carried out using the practical statistical package STATISTICA.

Research results. Neurological symptoms in most patients were due to focal lesions of one of the cerebral hemispheres. So, in MG-1 in 56.3% (27) patients in the left hemisphere, the focus was in 43.8% (21) of patients in the right hemisphere. In patients in MG-2, the focus of ischemia was localized in 18 (61.5%) patients - in the left hemisphere and in 40.0% (12) patients - in the right hemisphere of the brain (Table 6.2). In CG-1 right hemispheric stroke (RHS) LHS was in 13 patients (56.5%), RHS was in 10 patients (43.5%), CG-2 LHS was detected in 11 patients 952.4%), and RHS was in 10 (47.6%) patients (vol. 2).

**Table 2.**

**Distribution of patients in subgroups depending on the focus**

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| | subgroups | total | | RHS | | LHS | |
|---|---|---|---|---|---|---|---|
| | | abc | % | abc | % | abc | % |
| 78 | MG-1 | 48 | 61,5% | 27 | 56,3% | 21 | 43,8% |
| 78 | MG -2 | 30 | 38,5% | 18 | 60,0% | 12 | 40,0% |
| 122 | **total** | **78** | **63,9%** | **45** | **57,7%** | **33** | **42,3%** |
| 44 | CG-1 | 23 | 52,3% | 13 | 56,5% | 10 | 43,5% |
| 44 | CG-2 | 21 | 47,7% | 11 | 52,4% | 10 | 47,6% |
| 122 | **total** | **44** | **36,1%** | **24** | **54,5%** | **20** | **45,5%** |
| 122 | ***total*** | ***122*** | ***100,0%*** | ***69*** | ***56,6%*** | ***53*** | ***43,4%*** |

**Note: RHS - right hemisphere stroke, LHS - left hemisphere stroke.**

In general, neurological symptoms and severity of IS were more pronounced in MG compared to CG, which can be explained by the presence in OH patients of a new risk factor for endothelial dysfunction - COVID-19.

The dynamics of neurological symptoms before and after treatment in the MG and HC is shown in Table 3.

When examining the cranial nerves (CN), gaze paresis was noted in 13 (27.1%) in MG-1, in 7 (23.3%) in MG-2, in 9 (18.8%) in CG-1 and in 5 (16.7%) in CG-2, which regressed after treatment in all patients. In earlier periods, gaze paresis leveled out in patients of the CG-1 subgroup.

Neurological symptoms associated with the appearance of a lesion in the brain were presented, first of all, by signs of damage to the pyramidal tract on the side opposite to the affected hemisphere. Thus, central paresis of the VII pair - in the form of smoothing of the nasolabial fold and the impossibility of performing lower facial tests was detected in 45 (93.8%) in MG-1, in 26 (86.7%) in MG-2, in 20 (87 0%) in CG-1 and in 18 (85.7%) in HC-2, which after treatment regressed to HC on the background of neuroprotective therapy (subgroup CG-1) much faster. The regression of neurological symptoms in MG-1 was more effective than in MG-2 with a significant difference in the "gain of improvement"-Δ for many symptoms (t.6.3).

Hemiparesis of varying severity or hemiplegia was present in a large number of patients, since we took severe subtypes of IS-AT and CE to study the dynamics of neurological symptoms. Thus, mild hemiparesis was detected in 10 (20.8%) in MG-1, in 6 (20.0%) in MG-2, in 7 (30.4%) in CG-1 and in 7 (33, 3%) in CG-2, as seen in Table 6.3. mild paresis was more common in CG patients than in MG patients ($p<0.05$). Severe hemiparesis was detected in 17 (35.4%) in MG-1, in 12 (40.0%) in MG-2, in 8 (34.8%) in CG-1 and in 8 (38.1%) in CG-2. Hemiplegia was in a fairly large number of patients in the MG compared with the CG. Thus, hemiplegia was detected

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in 21 (43.8%) in MG-1, in 12 (40.0%) in MG-2, in 8 (34.8%) in CG-1 and in 6 (28.6%) %) in CG-2.

**Table 3.**

**Dynamics of neurological symptoms in patients with IS during treatment, depending on the history of COVID-19.**

| Symptoms | MG -1 (n=48) | | | | Δ | MG-2 (n=30) | | | | Δ | p< | p< |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | before tratment | | after tre-mnt | | | before trat-nt | | | | | | |
| | abc | % | abc | % | 1 | abc | % | abc | % | 2 | 1--2 | 1--3 |
| Paresis of the gaze | 13 | 27,1% | 0 | 0,0% | 27,1% | 7 | 23,3% | 0 | 0,0% | 23,3% | 0,05 | 0,05 |
| Central paresis of the VII pair of CNs | 45 | 93,8% | 32 | 66,7% | 27,1% | 26 | 86,7% | 23 | 76,7% | 10,0% | 0,005 | 0,005 |
| Central paresis of the XII pair of CNs | 41 | 85,4% | 29 | 60,4% | 25,0% | 26 | 86,7% | 22 | 73,3% | 13,3% | 0,005 | 0,05 |
| A phasia | 10 | 20,8% | 5 | 10,4% | 10,4% | 6 | 20,0% | 4 | 13,3% | 6,7% | | |
| Mild hemiparesis | 10 | 20,8% | 16 | 33,3% | -12,5% | 6 | 20,0% | 10 | 33,3% | -13,3% | | 0,05 |
| Severe hemiparesis | 17 | 35,4% | 23 | 47,9% | -12,5% | 12 | 40,0% | 13 | 43,3% | -3,3% | 0,005 | 0,05 |
| Hemiplegia | 21 | 43,8% | 9 | 18,8% | 25,0% | 12 | 40,0% | 7 | 23,3% | 16,7% | 0,05 | 0,05 |
| Pathological reflex | 46 | 95,8% | 38 | 79,2% | 16,7% | 29 | 96,7% | 26 | 86,7% | 10,0% | | 0,05 |
| Hemihypesthesia | 42 | 87,5% | 30 | 62,5% | 25,0% | 24 | 80,0% | 20 | 66,7% | 13,3% | 0,05 | 0,05 |
| Vilolation of functions of the pelvic organs | 7 | 14,6% | 1 | 2,1% | 12,5% | 4 | 13,3% | 1 | 3,3% | 10,0% | 0,05 | |
| **Symptoms** | **CG-1 (n=23)** | | | | **Δ** | **CG-2 (n=21)** | | | | **Δ** | **p<** | **p<** |
| | before tratment | | after tre-mnt | | | before tratment | | after tre-mnt | | | | |
| | abc | % | abc | % | 3 | abc. | % | abc | % | 4 | 3--4 | 2--4 |
| Paresis of the gaze | 9 | 18,8% | 0 | 0,0% | 18,8% | 5 | 16,7% | 0 | 0,0% | 16,7% | | 0,05 |
| Central paresis of the VII pair of CNs | 20 | 87,0% | 16 | 69,6% | 17,4% | 18 | 85,7% | 15 | 71,4% | 14,3% | 0,05 | |
| Central paresis of the XII pair of CNs | 19 | 82,6% | 14 | 60,9% | 21,7% | 18 | 85,7% | 14 | 66,7% | 19,0% | | 0,05 |
| A phasia | 4 | 17,4% | 2 | 8,7% | 8,7% | 5 | 23,8% | 2 | 9,5% | 14,3% | 0,005 | 0,005 |
| Mild hemiparesis | 7 | 30,4% | 9 | 39,1% | -8,7% | 7 | 33,3% | 8 | 38,1% | -4,8% | | 0,005 |
| Severe hemiparesis | 8 | 34,8% | 10 | 43,5% | -8,7% | 8 | 38,1% | 10 | 47,6% | -9,5% | 0,05 | |
| Hemiplegia | 8 | 34,8% | 4 | 17,4% | 17,4% | 6 | 28,6% | 3 | 14,3% | 14,3% | 0,05 | |
| Pathological reflexes | 20 | 87,0% | 16 | 69,6% | 17,4% | 18 | 85,7% | 15 | 71,4% | 14,3% | 0,05 | 0,05 |
| Hemihypesthesia | 19 | 82,6% | 16 | 69,6% | 13,0% | 17 | 81,0% | 16 | 76,2% | 4,8% | 0,05 | 0,05 |
| Dysfunction of the pelvic organs | 3 | 13,0% | 0 | 0,0% | 13,0% | 3 | 14,3% | 1 | 4,8% | 9,5% | | |

**Hereinafter - Note: Δ - dynamics of improvement in symptoms during treatment (%). "After treatment" - examination after 90 days.**

During treatment, many patients experienced a transformation of severe hemiparesis and hemiplegia into mild hemiparesis and severe hemiparesis, respectively. "Increase in improvement" - Δ in subgroups MG-1 and CG-1 was greater compared to subgroups MG-2 and CG-2, respectively, and had significant differences (v.3).

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Pathological reflexes were characteristic of most of the examined patients: in 46 (95.8%) in MG-1, in 29 (96.7%) in MG-2, in 20 (86.9%) in CG-1 and in 18 (85.7%) in CG-2. After treatment, the percentage of patients with pathological reflexes decreased in MG-1 by 25.0%, in MG-2 by 13.3%, in CG-1 by 17.4%, in CG-2 by 14.3%. With significant differences between subgroups MG-1 and MG-2 and CG-1 and CG-2.

Among other focal neurological symptoms in the examined patients, there were violations of sensitivity on the side opposite to the affected hemisphere - in 42 (87.5%) in MG-1, in 24 (80.0%) in MG-2, in 19 (82.6%) %) in CG-1 and in 17 (81.0%) in CG-2. In the dynamics against the background of treatment, there was an improvement in symptoms (hemihypesthesia regressed) by 16.7% in MG-1, by 13.3% in MG-2, by 13.0% in CG-1 and by 4.5% in CG-1. 2. Significantly good regression of hemihypesia was observed in subgroups with the addition of neuroprotective therapy (v.3). Meningeal symptoms were not detected in patients.

Dysfunction of the pelvic organs was expressed in urination disorders in the form of urinary incontinence of central origin, stool retention and was observed in 7 (14.6%) in MG-1, in 4 (13.3%) in MG-2, in 3 (20, 8%) in CG-1 and 5 (23.8%) in CG-2. Improvement of this symptomatology in MG-1 was observed by 12.5%, in MG-2 by 13.0%, in CG-1 by 9.5%. There were no significant differences in this category of symptoms.

Cortical speech disorders were observed in 10 (20.8%) in MG-1, in 5 (10.4%) in MG-2, in 4 (17.4%) in CG-1 and in 5 (23.8% ) in CG-2. On the background of treatment, a good dynamics was observed in the subgroups MG-1 and CG-2 ($p<0.05$).

According to the research results, it can be noted that the transferred COVID-19 slowed down the recovery of impaired functions, which is especially evident in MG-2 compared to CG-2, despite standard therapy and exercise therapy. During treatment with the addition of neuroprotective therapy, there was an improvement in symptoms in both groups with significant differences in many symptoms.

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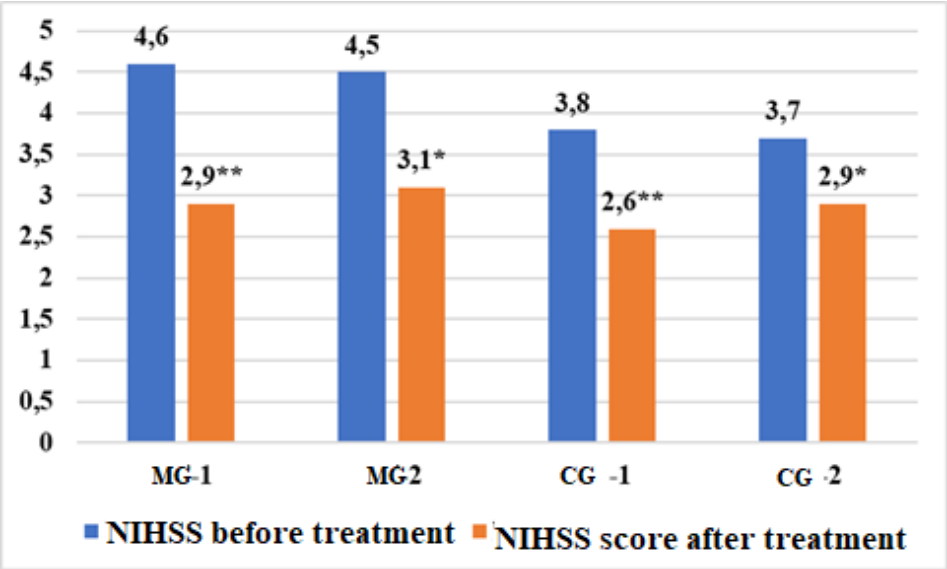


**Здесь и далее: Примечание: достоверность различий * - p < 0,05; **- p < 0,005.**

**Figure 1. Dynamics of indicators on the Rankin scale over the observation period.**

According to the Rankin scale in MG-1 and MG-2 there were initially high scores -4.6+1.2 and 4.5+1.1 points, respectively. During treatment, the scores significantly decreased to 2.9+0.2 and 3.1+0.5, respectively. Prior to treatment in the acute period, the Rankin scores in CG-1 and CG-2 were significantly lower compared to MG-1 and MG-2. But after treatment, positive dynamics was also observed in these subgroups, and based on Figure 1, in groups where patients received additional neuroprotective therapy, a rapid and significant regression of symptoms was observed.

According to the NIHSS scale used to determine the level of neurological deficit in MG-1 and MG-2, the following indicators were initially -23.52 and 23.68 points, respectively. In the dynamics against the background of treatment, the indicators improved, this was especially noticeable in the MG-1 subgroup ($p<0.005$) - 16.47 and 17.61, respectively. In subgroups CG-1 and CG-2, the NIHSS scores were 18.23 and 18.59 points, respectively, after rehabilitation measures - 14.28 and 15.12 points, respectively. In these subgroups, it is also noticeable that patients on the background of neuroprotection showed better results on the NIHSS scale.

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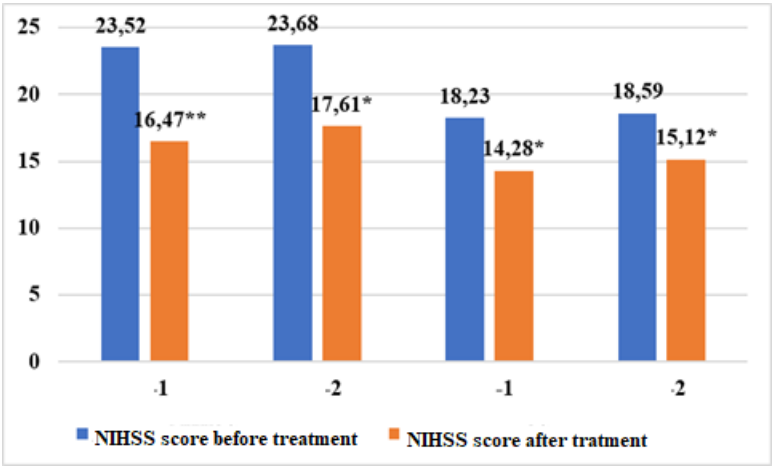


**Figure 2. Dynamics of changes in indicators on a scale over the observation period.**

According to the MoCA scale in the MG-1 mental status assessment conducted after treatment, the average value of the indicator is 20.3 ± 1.8 points, which corresponds to moderate cognitive impairment and is (20.5 ± 2.17) (Fig. 3) . When ranking the results of the MoCA scale for assessing the mental status in MG-1, the test result significantly improved - 24.6+1.3 points ($p<0.05$).

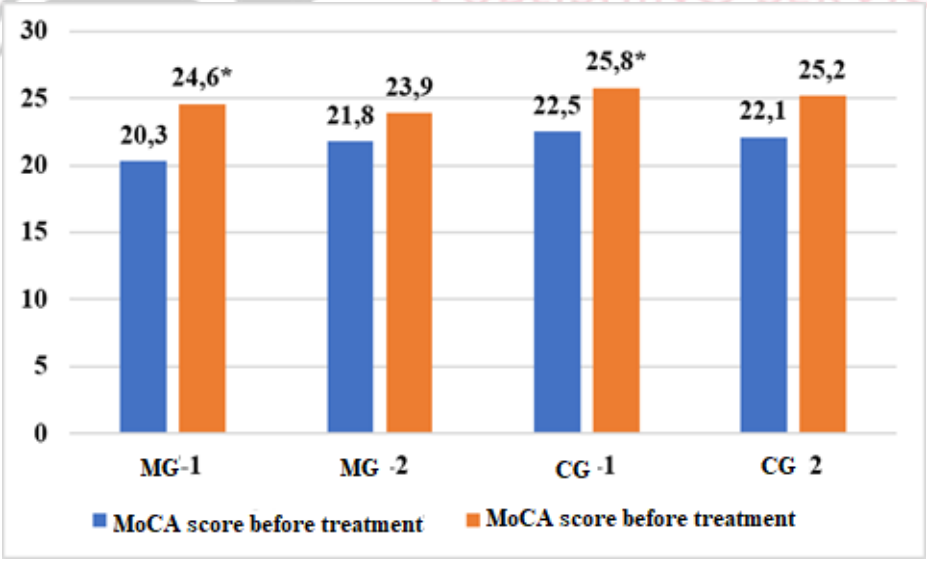


**Figure 3. Dynamics of changes in indicators on the MoCa scale for the observation period.**

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In MG-2, there was also a positive dynamics of the results of the MoCA scale before and after treatment - 21.8+1.6 and 23.9+0.9 points, no significant differences were found. In CG-1 and CG-2, initially the results of the MoCA scale were 22.5+1.8 and 22.1+1.2 points, respectively. During the treatment, positive dynamics was also observed - 25.8+1.5 and 25.2+1.7, respectively, no significant differences were found (Fig. 3).

When detailing the results of testing on the MoCA scale, in general, the examined patients were dominated by changes in the executive function of drawing a broken line, optical-spatial disorders, and worsening of delayed word reproduction (hearing-speech memory). At the same time, auditory-verbal memory disorders were more often observed in patients with MG.

**Table 4**

**Dynamics of changes in indicators on the MoCa scale (detailed)**

| Indicators | MG-1 (n=48) | | | | | MG -2 (n=30) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | before treatment | | p< | after treatment | | before treatment | | p< | after treatment | |
| | abc | % | | abc | % | abc | % | | abc | % |
| Visual-constructive praxis | 20 | 41,7% | 0,005 | 12 | 25,0% | 12 | 40,0% | 0,05 | 8 | 26,7% |
| Name of images | 20 | 41,7% | 0,005 | 10 | 20,8% | 13 | 43,3% | 0,05 | 9 | 30,0% |
| Attention | 28 | 58,3% | 0,005 | 16 | 33,3% | 17 | 56,7% | 0,05 | 11 | 36,7% |
| Speech | 13 | 27,1% | 0,005 | 5 | 10,4% | 8 | 26,7% | 0,05 | 4 | 13,3% |
| Abstraction | 25 | 52,1% | 0,005 | 13 | 27,1% | 15 | 50,0% | 0,05 | 9 | 30,0% |
| Delayed playback | 29 | 60,4% | 0,005 | 19 | 39,6% | 18 | 60,0% | 0,05 | 12 | 40,0% |
| Orientation | 6 | 12,5% | 0,005 | 3 | 6,3% | 4 | 13,3% | 0,05 | 1 | 3,3% |
| Indicators | CG -1 (n=23) | | | | | CG -2 (n=21) | | | | |
| | before treatment | | p< | after treatment | | before treatment | | p< | after treatment | |
| | abc | % | | abc | % | abc | % | | abc | % |
| Visual-constructive praxis | 8 | 34,8% | 0,005 | 5 | 21,7% | 8 | 38,1% | 0,05 | 6 | 28,6% |
| Name of images | 6 | 26,1% | 0,005 | 6 | 26,1% | 7 | 33,3% | 0,05 | 5 | 23,8% |
| Attention | 6 | 26,1% | 0,005 | 4 | 17,4% | 8 | 38,1% | | 7 | 33,3% |
| Speech | 5 | 21,7% | 0,005 | 3 | 13,0% | 7 | 33,3% | 0,05 | 4 | 19,0% |
| Abstraction | 8 | 34,8% | 0,005 | 4 | 17,4% | 9 | 42,9% | 0,05 | 5 | 23,8% |
| Delayed playback | 4 | 17,4% | | 2 | 8,7% | 6 | 28,6% | | 5 | 23,8% |
| About orientation | 2 | 8,7% | 0,005 | 0 | 0,0% | 2 | 9,5% | 0,05 | 0 | 0,0% |

In the MG, psycho-emotional disorders were more common in the form of dysphoria, irritability, demonstrative behavior, a decrease in the level of attention and faster exhaustion when performing a task.

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When detailing the results of the MoCa scale for assessing the mental status in MG-1, cognitive impairments were observed in a larger number of patients in the categories "Visual-constructive praxis", "Name of images", "Attention", "Speech", "Abstraction", "Delayed reproduction", "Orientation"- 41.7%, 41.7%, 58.3%, 27.1%, 52.1%, 60.4%, 12.5%, respectively, which is significantly more frequent compared to CG-1, where for these categories, the distribution of percentages was as follows - 34.8%, 26.1%, 26.1%, 21.7%, 34.8%, 17.4%, 8.7%, respectively ($p < 0.05$). Against the background of treatment in subgroups of patients who received neuroprotective therapy, positive dynamics was observed in a larger number of patients compared with subgroups of both groups, where only standard therapy was used (t.4).

## CONCLUSION

Thus, the results of the study of indicators of neurological status and cognitive sphere showed that patients with hemispheric ischemic stroke who underwent COVID-19 have more pronounced neurological symptoms and cognitive deficits. Three months after treatment, patients with hemispheric ischemic stroke who received neuroprotective therapy showed a significant trend towards a decrease in cognitive deficit in patients in the recovery period of an ischemic stroke. In the subgroups of patients who were on standard therapy, a slower dynamics of recovery of the neurological status and cognitive sphere was observed. Probably, such a not so pronounced picture of recovery was associated with insufficient standard treatment for this category of patients, due to the aggravation of the transferred COVID-19.

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