

# Effectiveness of combined neurometabolic therapy in complex treatment of patients with hemorrhagic hemispheric stroke in recovery period

Anastasiia Dronova

Zaporizhzhia State Medical University, Zaporizhzhia, Ukraine

## ABSTRACT

**Objective.** The aim of this work was to estimate the effectiveness of combination neurometabolic therapy that includes 5 mg of ipidacrine hydrochloride and 300 mg of phenibut in complex therapy of patients with hemisphere hemorrhagic stroke in the early rehabilitation period.

**Material and methods.** Open comparative randomized study and treatment of 46 patients (31 men and 15 women) with hemisphere hemorrhagic stroke in the early rehabilitation period was performed. The mean age of patients was 57.17 ± 7.09 years. All patients were divided into two groups - the main group included 20 patients with hemorrhagic stroke, who took neurometabolic combination therapy (5 mg of ipidacrine hydrochloride and 300 mg of phenibut three times per day) in addition to complex recovery treatment during 30 days (start from 30th day after stroke) and control group, that included 26 patients with hemorrhagic stroke, who received standard complex recovery treatment without additional neurometabolic therapy.

**Outcomes.** The median MoCA score of the main group of patients was 21.0 (19; 24), while the second group had 20.5 (18; 23.75) MoCA score, but without any intergroup difference. It was also identified reliable improvement of cognitive values on the MoCA scale after treatment ( $p < 0.05$ ). Besides, statistical difference was reached between groups in these measures. Also, we showed that statistical improvement in memory was observed in both groups at 1st and 2nd attempts using Luriya's method "memorizing 10 words". But subsequent such an effect took place only in the main group. The present study showed the absence of improvement "memorizing of 10 words" at 3rd, 4th and 5th attempts in control group. At the same time, patients of the main group had improved results at 4th and 5th ones ( $p < 0.05$ ).

**Conclusion.** The combined drug of neurometabolic nature, consisting of 5 mg ipidacrinum and phenibut 300 mg, improved rehabilitation effectiveness rates for account of cognitive functions in patients with hemorrhagic hemispheric stroke during recovery period during comprehensive rehabilitation.

**Keywords:** hemorrhage stroke, recovery period, rehabilitation, neurometabolic therapy

## INTRODUCTION

According to World Health Organization data, stroke is the second leading cause of death apart from cardiovascular pathology, and the fifth leading cause of disability. Moreover, an increase in disability levels among stroke patients has been observed in the last 20 years [1].

Not only motional or speech deficit is a reason of disability among stroke patients, but also a cogni-

tive decline. It has been reported by many studies that cognitive impairment impacts recovery process course and treatment effectiveness [2-5].

Searching for new and more effective methods of rehabilitation is one of the essential tasks for modern medicine [6-8]. Pharmaceutical and non-pharmaceutical therapy impact on the speech, motion and cognitive recovery dynamic is exploring [7-14].

Corresponding author:

Anastasiia Dronova

E-mail: anastas.drnv@gmail.com

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The majority of works searching for effective pharmacological agents is based on ischemic stroke studies [9-14], but considering different pathogenic mechanisms of ischemic and hemorrhagic stroke development it is relevant to study treatment effectiveness among patients with intracerebral hemorrhage. Careful assessment of pharmaceutical therapy impact on recovery course will allow making more differential prescription in the future without causing polypragmasia. Using of the combination drugs makes easier its taking for patients and increases effect of its individual components, that allows gaining better compliance and treatment result.

We paid attention to combination neurometabolic drug that includes 5 mg of ipidacrine hydrochloride and 300 mg of phenibut. Ipidacrine is a reversible acetylcholinesterase inhibitor that stimulates neuronal and neuromuscular conduction and blocks sodium permeability of cell membrane, whereas phenibut has a positive effect on metabolic processes in cerebral neurons [8].

### Objective

The aim of this work was to estimate the effectiveness of combination neurometabolic therapy that includes 5 mg of ipidacrine hydrochloride and 300 mg of phenibut in complex therapy of patients with hemisphere hemorrhagic stroke in the early rehabilitation period.

## MATERIAL AND METHODS

Open comparative randomized study of 46 patients (31 men and 15 women) with hemisphere hemorrhagic stroke in the early rehabilitation period was performed in Zaporizhzhia State Medical University neurological clinic. The age of patients varied from 35 to 75 years (mean age was  $57.17 \pm 7.09$  years). Inclusion criteria were the next: patients with diagnosis of hemisphere hemorrhagic stroke (confirmed by CT); patients who were recommended conservative treatment by neurosurgeon; patients at the beginning of early rehabilitation period (30th day after stroke) and those who signed research participation agreement form. Exclusion criteria were: repeated stroke, patients with two or more lesions according to CT data, patients after surgical treatment of stroke, patients with consciousness impairment, psychological disorders, significant aphasia, cancer pathology, alcoholic addiction, severe somatic pathology that can hinder active rehabilitation and brain injury in the past. All patients before and after treatment were examined with specially designed protocol, which included assessment of the neurological, cognitive and psychoemotional status of hemorrhagic stroke patients in the early rehabilitation period. Neurologi-

cal examination was held using National Institutes of Health Stroke Scale (NIHSS) for identification of neurological deficit, Modified Rankin Scale (mRS) for assessment of functional recovery level and Barthel ADL Index (BI) for measuring performance in activities of daily living. Assessment of cognitive function was performed using Mini-Mental state examination (MMSE) and Montreal Cognitive Assessment (MoCA), also memory function was assessed by method A. R. Luria's "memorizing 10 words" and questionnaire for memory self-assessment (McNair and Kahn). Psychoemotional state was estimated with Beck's Depression Inventory and State-Trait Anxiety Inventory (STAI).

All patients were divided into two groups - main and control. The main group included 20 patients with hemorrhagic stroke (13 men (65%) and 7 women (35%) mean age was  $57.1 \pm 8.01$  years), who took neurometabolic combination drug (5 mg of ipidacrine hydrochloride and 300 mg of phenibut three times a day) in addition to complex recovery treatment during 30ty days (start from 30th day after stroke). Control group included 26 patients (18 men (69.23%) 8 women (30.77%) mean age was  $57.23 \pm 6.38$  years) with hemorrhagic stroke, who received standard complex recovery treatment without additional neurometabolic therapy. Standard recovery treatment included: pharmacotherapy (pathogenic (anti-hypertensive drugs, remedies that increase coronary artery blood flow and heart muscle metabolism, antiarrhythmic and antidiabetic), medications for increasing cerebral metabolism and microcirculation, symptomatic therapy (analgesics, muscle relaxants)), movement therapy (body position treatment, individual exercises, training of walking, physical therapy with the table exercise machine for wrist and fingers, special technics for decreasing muscle tonus), physiotherapy (segmental zone massage, limbs massage, physiotherapy with apparatus), psychotherapy, speech therapy if it was needed.

Statistical analysis of results was performed using Statistica 13.0 software (StatSoft Inc., № JP-Z804I382130ARCN10-J). Results presented as a median and interquartile range (Me, Q25; Q75). For comparison studied indicators in different groups Mann — Whitney U-test was used. For assessment studied indicators before and after treatment in the same group Wilcoxon signed-rank test was used. Reliable results were considered at  $p < 0.05$ .

## OUTCOMES

Both groups of adults with stroke did not differ significantly in sex, age, stroke site, and neurological deficit on the 30<sup>th</sup> day after the cerebrovascular accident. Neurological examination of the patients is also shown in table 1.

**TABLE 1.** Clinical and neurological characteristics of patients with hemorrhagic hemispheric stroke on the 30<sup>th</sup> day after stroke

Indicator	Main group (n = 20)	Control group (n = 26)	p
Age, years	57.1±8.01	57.23±6.38	0.54905
Sex	13 males (65.0%) 7 females (35.0%)	18 males (69.23%) 8 females (30.77%)	0.81602
Site of lesion (dominant hemisphere / subdominant hemisphere)	11 (55.0%) / 9 (45.0%)	18 (69.3%) / 8 (30.7%)	0.18736
NIHSS (Me (Q25; Q75))	7.5 (5; 9.25)	8 (4.25;9.75)	0.43802
mRS (Me (Q25; Q75))	3 (2; 3)	3 (2; 3)	0.98119
BI (Me (Q25; Q75))	80 (68.75; 90)	75 (65; 88.75)	0.99014

The main group of patients had NIHSS score of 7.5 (5; 9.25) before treatment, while the control group of stroke survivors had NIHSS score of 8 (4.25;9.75), without reaching statistical significance ( $p > 0.05$ ). Substantial neurological improvement occurred in patients from two groups after treatment. In this way, the median NIHSS score of the main group of patients with HHS was 6 (4; 7.25) and of the control group – 6 (3.5; 7.75), ( $p < 0.05$ ). These discrepancies also did not reach statistical difference as before treatment. The baseline cognitive impairment on the MMSE scale is summarized in Table 2.

**TABLE 2.** Structure of cognitive impairment rates in main and control groups in patients with hemorrhagic hemispheric stroke before treatment

Cognitive impairment rates	Main group (n = 20)	Control group (n = 26)
Absence of cognitive impairment (MMSE 28-30)	2 (10.0%)	3 (11.54%)
Mild cognitive impairment (MMSE 26-27)	8 (40.0%)	8 (30.77%)
Moderate cognitive impairment (MMSE 24-25)	6 (30.0%)	10 (38.46%)
Mild dementia (MMSE 20-23)	4 (20.0%)	5 (19.23%)

Before treating, the patients of main group had the median MMSE score of 25.5 (24.5; 27) and the

patients of the control one – 25 (24; 27), without significant difference between groups. After treatment, both groups of patient with HHS met improvement. The first group had 26 (24.25; 27) MMSE score and the second one – 26 (25; 27.25), respectively ( $p < 0.05$ ).

Among 45 patients with hemorrhagic hemispheric stroke out of 46 MoCA scores were skewed toward lower values in early observations. The median MoCA score of the first group of patients was 21.0 (19; 24), while the second group had 20.5 (18; 23.75) MoCA score, but without any intergroup difference.

It was also identified reliable improvement of cognitive values on the MoCA scale after treatment ( $p < 0.05$ ). Besides, statistical difference was reached between groups in these measures. Table 3 displays dynamics of level cognitive functions on MoCA scores.

Our results demonstrated that improvement mainly occurred in the visuospatial, language and memory domains in both groups, ( $p < 0.05$ ). Increment in attention domain took place only in stroke survivors of the main group, ( $p < 0.05$ ).

Also, we showed that statistical improvement in memory was observed in both groups at 1st and 2nd attempts using Luriya's method "memorizing 10 words". But subsequent such an effect took place

**TABLE 3.** Dynamics of cognitive functions on MoCA scale patients with hemorrhagic hemispheric stroke in recovery period

Domain	Study group, Score Me (Q25; Q75)			
	Main group (n = 20)		Control group (n = 26)	
	Before treatment	After treatment	Before treatment	After treatment
Visuospatial	3 (2; 4)	3.5 (3; 4) *	3 (2; 4)	3 (3; 4) *
Naming	3 (3; 3)	3 (3; 3)	3 (3; 3)	3 (3; 3)
Attention	5 (4; 5.25)	5 (4; 6) *	5 (4; 5)	5 (3.25; 5)
Language	2 (1; 2)	2 (1; 2) *	1 (1; 2)	1.5 (1; 2) *
Abstraction	2 (1; 2)	2 (1.75; 2)	2 (1; 2)	2 (1; 2)
Memory	2 (1; 2)	2 (2; 3) *	1.5 (1; 2)	2 (2; 2) *
Orientation	6 (5; 6)	6 (5.75; 6)	5.5 (5; 6)	6 (5; 6)
Overall score	21 (19; 24)	23.5 (21.75; 25)**	20.5 (18; 23.75)	21.5 (19; 24) *

\* - reliable improvement on the 30<sup>th</sup> day after stroke,  $p < 0.05$ ; # - reliable improvement by comparison to control group,  $p < 0.05$ .

**TABLE 4.** Rates of Luriya’s method “memorizing 10 words” in dynamics in patients with hemorrhagic hemispheric stroke in recovery period

Attempt	Study group, Score Me (Q25; Q75)			
	Main group (n = 20)		Control group (n = 26)	
	Before treatment	After treatment	Before treatment	After treatment
1 <sup>st</sup> attempt	5 (4; 6)	5 (5; 6) *	4.5 (4; 5)	5 (4; 5.75) *
2 <sup>nd</sup> attempt	5 (5; 7)	6 (5; 7) *	5 (4; 7)	5 (5; 7) *
3 <sup>rd</sup> attempt	6 (5; 8)	7 (6; 8)	6 (5; 7.75)	6 (5; 7)
4 <sup>th</sup> attempt	7 (5.75; 8)	7 (6; 9) *	7 (6; 8)	7 (6; 8)
5 <sup>th</sup> attempt	7 (6; 9)	8 (7; 9.25) *	7 (6; 8.75)	7 (6; 9)

\* - reliable improvement by comparison to the 30<sup>th</sup> day after stroke,  $p < 0.05$

only in the main group. The present study showed the absence of improvement “memorizing of 10 words” at 3rd, 4th and 5th attempts in control group. At the same time, patients of the main group had stable outcomes at 3rd attempt and improved results at 4th and 5th ones, which met statistical differences ( $p < 0.05$ ). The summarized results are shown in table 4.

The results of the experiment found clear support that patients in the control group had lower levels of attention, and concentration, as well as more exhaustion rates in comparison to main group values.

We described the results of memory self-assessment tests over time, which showed that only main group patients had positive trends in evaluation. Therefore, the median of the test was 37.5 (23.5; 41.5) on the 30th day after stroke, while the after treatment value was 34.5 (22.5; 40.25) ( $p < 0.05$ ). At the time, there was not any statistical difference met in the medians of memory self-assessment test in stroke patients of the second group, which were as follows – 36 (29; 39.75) before treatment and 32 (23.75; 40) after treatment, without statistical difference ( $p > 0.05$ ).

The level of state anxiety and trait anxiety before treatment on Spielberger scale in patients of the first group were 48 (44.25; 50.5) and 41.5 (36.75; 47.75), respectively. The values for the second group were as follows – 47 (41.25; 48) and 45 (38; 51.5) respectively, without statistical difference ( $p > 0.05$ ).

As a result, the after treatment state anxiety level in the experimental group was 47.5 (39.25; 50.5) and trait anxiety one was 45 (38; 49.5). In control group the value was 47 (41.25; 48) and 45 (38; 51.5). Such discrepancies did not reach any statistical difference between groups, and in the groups after treatment.

The results did not provide any evidence of a reliable difference in both groups using Beck’s Depression Inventory (BDI). Thus, the median of the scale of the experimental group of patients was 37 (31.25; 42) before treatment, and 38 (33.25; 42) after

treatment, respectively. At the control group of patients after stroke had BDI median of 38 (29.25; 41) before treatment and 38 (31.5; 39) after care ( $p > 0.05$ ).

## DISCUSSION

Question of searching for effective methods and tools of post-stroke motor and cognitive impairment rehabilitation is still open today. The majority of works is searching in the direction of non-pharmaceutical treatment [9-15], some of them are dedicated to exploration of pharmaceutical therapy effectiveness [7,8,16-19].

In the works that dedicated to pharmaceutical treatment of stroke effectiveness of using injectable medication, that patients receive at the hospital during acute period is analyzed more often [16,18,20]. Some of the medications from these studies [16,18] have shown positive effect on cognitive function among post stroke patients. One of them, a preparation called “Reneuro”, that was used in combination with other drugs, had the similar action as ipidacrine – boosting function of neuronal conduction.

In certain studies, there was no reliable effect in case of using such medications [7] at subarachnoid hemorrhage.

Works that were dedicated to combination of ipidacrine and phenibut were performed in group of patients with ischemic stroke at the later period of treatment (at least three months from disease occurrence) [19]. Moreover, in this study patients with lower MMSE score were included. Mean age in a cohort were higher, then mean age of patients in our study. In spite of this differences in both studies positive results after treatment were received. Results which we received to some extent are similar to findings of other researches, that indicate improvement of the level of attention and memory among patients diagnosed with hemorrhagic stroke.

In a study from 2021 was proven more rapid recovery of cognitive functions among patients with

hemorrhagic stroke than among patients with ischemic stroke [21], that also could impact study results.

Therefore, performed study proves high effectiveness of ipidacrine and phenibut capsule combination, convenience of its ambulatory using during recovery period of hemorrhagic stroke.

## CONCLUSIONS

The combined drug of neurometabolic nature, consisted of 5 mg ipidacrinum and phenibut 300 mg, improved rehabilitation effectiveness rates for account of cognitive functions in patients with hem-

orrhagic hemispheric stroke during recovery period during comprehensive rehabilitation.

Ipidacrinum and phenibut in combination better improved refinement of memory and awareness. The preparation provided greater rates of memorizing during tests objectively and a positive impact on memory subjectively.

There was not reached any statistical improvement of neurometabolic therapy on the anxiety and depression disorders.

Future research should consider the potential effects of combined neurometabolic therapy in patients with hemorrhagic hemispheric stroke in the late recovery period.

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