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PHARMACOECONOMIC ANALYSIS OF TREATMENT OF PATIENTS WITH SEVERE AND MODERATE ISCHEMIC STROKE (NIHSS SCORE > 12)

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Abstract: *this study includes pharmacoeconomic analysis of treatment of patients with severe and moderate ischemic stroke (NIHSS score > 12). The results of data search showed that today an evidential base for these patients treatment exists for cerebrolysin only. The analysis of «budget impact» showed that the transfer of one patient from the basic therapy to the combined therapy with cerebrolysin using gives saving of about 79703 rubles. Therefore the analysis of «costs-efficiency» ratio for the basic therapy with cerebrolysin using demonstrated it to be a dominated technology in comparison with the basic therapy only.*

Key words: *efficiency analysis, costs analysis, analysis of «costs-efficiency» ratio, analysis of «budget impact», ischemic stroke, severe and moderate disease level, cerebrolysin, pharmacoeconomy, clinical and economic analysis.*

Introduction

Ischemic stroke (IS) is a clinical syndrome manifesting as an acute disorder of local cerebral functions which lasts for more than 24 hours or causes death; it can be caused either by insufficiency of blood supply in certain brain area due to cerebral blood flow reduction, thrombosis or embolism connected with vascular, cardiac or blood diseases [1, 2].

About 16 million cases of stroke are registered in the world annually, including 5,7 million with lethal outcome which equals 10% of total mortality in the world [3-6]. It should be especially noted that sever and moderate ISs take about 40-65% and this category of patients is characterized with high mortality [7-10].

Today severe and moderate IS are one of the main causes of people disability. Expansion of disability of the patients suffered a stroke is caused by a small number of patients who were urgently admitted to hospital (not more than 15 — 30%). About one third of patients suffered a stroke are of working age [11]. Only 20% of patients remain socially and professionally adapted and not more than 10% return to their working activity [12, 133]. Nearly 20% of patients suffered a stroke remain seriously disabled for the rest life [144]. Moreover nearly 50% of patients require assistance and 30% need care [1]; so the stroke is a burden for the patient's family members reducing their labor potential and quality of life.

Therefore the stroke is an important medicinal and social problem. High level of morbidity, mortality, disability makes this disease an essential economic burden for the state and the society in general. Considering the current situation in the Russian Federation (RF) with limited health care resources, an optimization of medical care for the patients suffered severe and moderate IS is a priority task for the public health authorities in the context of the budget of the health care system [15]. A pharmacoeconomic assessment is one of the important tools for choosing the most effective therapy from both clinical and economic point of view. Therefore a pharmacoeconomic analysis of treatment of the patients suffered from severe and moderate IS (NIHSS score > 12) is interesting for the Russian health care system.

The goal of the investigation is a comparison of neuroprotective drugs in the context of pharmacoeconomic analysis: cerebrolysin, cortexin, actovegin, ceraxon, cytoflavin, cellex and mexidol for treatment of patients suffered from severe and moderate IS (NIHSS score > 12) on the basis of analysis of cost-efficiency ratio, drug safety and the quality of life of the patients.

Data search as a part of analysis of efficiency

To perform pharmacoeconomic investigation according to the above goal an analysis was performed. Data search by publications with the topic of the investigation was performed by database PubMed, Medlink, Cochrane. The search request was made in such a way that the found publication contained key words: "acute ischemic stroke", "clinical trial", "neuroprotective drugs", "stroke severity", "cerebrolysin", "cortexin", "actovegin", "ceraxon", "cytoflavin", "cellex", "mexidol". For the review of publications and data search was performed by database «Russian medicine » of I.M. Sechenov First Moscow State Medical University, scientific electronic library elibrary.ru, free searching resources like Yandex, Google etc. Data search included the following key words: "acute ischemic stroke", "brain infarction", "neuroprotective drugs", "efficiency", "clinical trial", "severity of stroke", "cortexin", "actovegin", "mexidol", "cellex", "ceraxon", "cytoflavin", "cerebrolysin".

There were found more than 3000 publications which met the request. Then the duplicate publications and trials not relating to the IS treatment with neuroprotective drugs were excluded; the analysis did not also include randomized clinical trials (RCT) where the compared medicinal drugs (MD) were assessed in combination with other not neuroprotective MD. The strength of recommendations was determined by the assessment scores of the strength of recommendations of the clinical trials results and the assessment of the evidence level of the MD clinical trials. The trials with evidence levels A or B were chosen first of all: proves summarized in the systematic review, meta-analysis and proves received in prospective RCTs respectively. If there are no such trials, then the trials with lower evidence levels were examined. The results were summarized in the table for analysis and were a subject of expert assessment. Thus 26 publications were selected for detailed analysis after screening (Table 1).

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Table 1. Summary table with description of publications on the trials of the efficiency of neuroprotective MD using at IS

No	MD	Source	Sampling size	Trial objects	Observation period	Efficacy criteria	Results	Comments
1	Cortexin (Polypeptides of cattle cortex)	[21]	62	1) cortexin 2) placebo	28 days	Scores: NIHSS, Rankin, Barthel index	There is an improvement of parameters assessed by the scores used in the trial. There are no data of statistically essential differences	Small sampling size, no randomization and statistical data processing
2		[22]	35	1) cortexin 2) placebo	15 days	Scores: NIHSS, Rankin, Barthel index	There is an improvement of parameters assessed by the scores used in the trial. There are no data of statistically essential differences	Small number of patients participated the trial, no randomization and statistical data processing
3		[23]	68	1) cortexin 2) placebo	10 days	Scores: Orgogozo, original Barthel index	There is an improvement of parameters assessed by the scores used in the trial. There are no data of statistically essential differences	Small number of patients participated the trial, no randomization and statistical data processing
4		[24]	115	1) cortexin 2) nootropil 3) cerebrolysin	10 days	Clinical and psychometric scores, adverse effects assessment	No adverse effects at therapy. There are no data of statistically essential differences	No randomization and statistical data processing, small number of patients participated the trial
5		[25, 26]	272	1) cortexin + cortexin 2) cortexin + placebo 3) placebo + placebo	70 days	Scores: NIHSS, Rankin, Barthel index, Rivermead index, mortality	An evident prevalence of patients with good functional recovery was observed in the 1st and the 2nd groups, but the level of the 2nd monthly mortality did not evidently differ between the compared groups.	Multicenter double blind placebo-controlled trial, included patients with moderate stroke (with NIHSS score 7)
6	Ceraxon (citocoline)	[27]	2279	1) citicoline 2) placebo	Not specified	Assessment of mortality, disability	Reducing of mortality or disability frequency	Meta-analysis with description of statistical processing methods, patients with ischemic and hemorrhagic stroke together
7		[28]	1652	1) citicoline 2) placebo	90 days	NIHSS score; modified RS score; Barthel index; mortality	Improvement of the state by the investigated criteria was in 25,2% patients from citicoline group and 20,2% patients from placebo group during 3 months of observation. Citicoline therapy provided no effect on mortality	Meta-analysis with description of statistical processing methods, patients with NIHSS score > 8
8		[29]	214	1) citicoline 500 mg 2) citicoline 2000 mg 3) placebo	84 days	Assessment of impaired tissue size	Increase of impaired tissue size on the 12th week of treatment was 84,7%,in placebo group, 34,0% in citicoline 500 mg per day group, 1,8% in citicoline 2000 mg per day group.	Surrogate endpoints were chosen for efficiency assessment

9		[30]	2298	1) citicoline 2) placebo	Not specified	NIHSS score; modified RS score; Barthel index	The trial was cancelled after processing of data for 2078 patients as there were no statistically essential differences by the criterion «recovery of lost functions». No differences between the compared groups were found concerning the safety indices	Prospective multicenter randomized trial with a big number of patients, no statistically essential differences
10		[31]	-	1) citicoline 2) placebo	Not specified	NIHSS score; modified RS score; Barthel index	Safety of citicoline is higher, efficiency levels of citicoline and placebo are comparable	Prospective multicenter randomized trial. Patients distribution is not specified
11		[32]	141	1) citicoline 2) basic therapy	21 days	Dynamics of neurological symptoms by Scandinavian stroke score and functional outcome of disease by Barthel index and modified Rankin score	Better recovery was observed in citicoline group. Efficiency of citicoline was evidently higher (p<0,05) in patients under 70 years old and when the drug was administrated in the first hours of disease.	Short observation period, not relevant resultse
12		[33]	60	1) ceraxon 2) neuroxon	15 days	Assessment of cognitive functions, assessment of safety	After treatment with citicolines (neuroxon and ceraxon) the state improved nearly in all patients, which was shown as a gradual regress of symptoms.	The received results are statistically insignificant
13		[34]	24	1) citicoline 2) basic therapy	45 days	Assessment of cognitive functionsй	Gradual regress of neurological disturbances, reduction of disability degree. Positive impact of citicoline on cognitive functions is observed	Short trial horizon, small sampling size
14	Actovegin	[35]	60	1) actovegin 2) mexidol	21 days	Assessment of duration of stay in the hospital, mortality	Assessment of duration of stay in the hospital did not reveal essential differences between eth groups (actovegin group – 27,4±3,4 days, mexidol group 26,7±2,9 days; p>0,05). Reduction of mortality was observed in actovegin group. In was 13,3% with therapy using actovegin and 23,3 % in mexidol group	Short trial horizon, small sampling size, no characteristics of examined patients (severity of stroke)
15		[36]	82	1) actovegin + citicoline 2) citicoline 3) basic therapy	21 days	Dynamics of neurological state, mortality	Combinative neuroprotective therapy with using citicoline and actovegin was more efficient in comparison with mono neuroprotection and basic therapy due to more fast and full regress of neurological deficit, improvement of clinical and social outcome, reduction of early patients mortality, modulation of cerebral functional activity	Complex therapy, short trial horizon, small sampling size were compared

16	Cytoflavin	[37]	600	1) cytoflavin 2) basic therapy	120 days	Mortality, average duration of stay in the hospital	Using of cytoflavin with basic therapy allows mortality reducing 2,3 times (7,6 against 17,3%), and average duration of stay in the hospital reduces from 28,2 to 23,5 days for placebo and citoflavin respectively	Double blind placebo-controlled multicenter trial, included patients with moderate stroke
17		[38]	70	1) cytoflavin 2) basic therapy	35 days	Scores: NIHSS, Rankin, Barthel index	Using of cytoflavin provided reduction of neurologic deficit and increase of the patients' ability for self-care	Score of stroke severity by NIHSS was 9, short observation period
18	Mexidol	[39]	51	1) mexidol 2) placebo	14 days	Scores: NIHSS, Rankin, Barthel index	Reliable upstream dynamics in regress of neurologic disorders by NIHHS score was revealed by the 14th day of disease in mexidol group in comparison with placebo group; functional recovery (dynamics of clinical Barthel index on the 21st day) was revealed in patients included to the trial during the first 6 hours of disease.	Short trial horizon, small number of patients included in trial
19		[40]	112	1) mexidol + gliatilin + basic therapy 2) basic therapy	10 days	Mortality, adverse reactions	Mortality in the basic and the control groups was 27 and 42 % on the 10th day respectively. Glialitin and mexidol caused no essential adverse reactions.	Complex therapy is compared, short trial horizon
20		[41]	116	1)Мексидол + ТЛТ 2)Стандартная терапия + ТЛТ	21 days	Degree of neurological deficit	Using of complex therapy with mexidol causes really faster normalization of indices of eh acute stage of disease, which correlates with the degree of neurologic deficit reduction	Efficiency of thrombolytic therapy was studied and also together with mexidol, short observation period, included patients had moderate severity by NIHSS score (8—12)
21		[42]	43	1) mexidol 2) placebo	Not specified	General clinical state	Anti-oxidant effect of mexidol provides positive nootropic, energy-tropic and vegeto-tropic effects simultaneously.	Patients with various strokes (ischemic, hemorrhagic, subarachnoid, supratentorial)
22	Cerebrolysin	[43]	1070 (252 patients with NIHSS > 12)	1) cerebrolysin 2) placebo	90 days	Mortality, scores: NIHSS, Rankin, Barthel index	Cumulative percent of died patients was 20,2% in placebo group and 10,5% in cerebrolysin group on the 90th day.	Double blind trial with placebo control, the results are statistically significant
23		[44]	60	1) cerebrolysin 10 ml 2) cerebrolysin 50 ml 3) placebo	Not specified	Score NIHSS, Barthel index; modified Rankin scale; Global clinical impression scale (GCI) Rating scale (KOS)	Faster recovery of neurologic function by NIHSS score and Barthel index of everyday activity was observed	Prospective randomized trial; small sampling size

24		[45]	47	1) cerebrolysin 2) placebo	28 days	NIHSS score, Barthel index, modified Rankin score, CGI	Trend for faster recovery by GCI scale was revealed in cerebrolysin group	Prospective randomized trial; small sampling size
25		[46]	146	1) cerebrolysin 2) placebo	90 days	Barthel index, GCI, Canadian neurologic scale	No statistically significant differences between the group were revealed	Prospective randomized trials. At baseline no significant differences between the groups were observed
26		[47]	119	1) cerebrolysin + alteplaza 2) placebo + alteplaza	90 days	Scales: NIHSS, Rankin, Barthel index, Glasgow scale	Faster functions recovery was observed by the data of rating scales on the 30th day No differences between the groups were observed on the 90th day	Prospective randomized double blind clinical trial with placebo control

Results and discussions

Cortexin

Systematic reviews and meta-analyzes of efficiency of cortexin at IS were not conducted. We have found a number of clinical trials of cortexin use in IS therapy.

A study of Skoromets et al. [21] was a prospective, multicenter, double-blind, placebo-controlled clinical study of the efficiency and safety of cortexin in acute period of new-onset hemispheric IS. This clinical trial included patients aged from 50 to 85 years, admitted to hospital on the 1st day of the disease onset. The trial did not include the patients with hemorrhagic stroke; complete regression of neurological symptoms during the first 24 hours after the disease onset; patients with acute myocardial infarction, evident cardiac, hepatic or renal failure; other diseases accompanying with severe violations of systemic hemodynamics and metabolism. All patients were divided into two groups by simple randomization. The patients of the first group (32 persons) received cortexin 20 mg daily intramuscularly for 10 days. The patients of the second group (30 persons) received basic therapy with placebo administration 20 mg daily intramuscularly for 10 days. The analysis of clinical manifestations in the patients with IS who received cortexin in the acute phase of the disease, showed its positive effect on both cerebral and focal neurological symptoms (NIHSS score). On the 3-7th day of treatment the patients who received cortexin demonstrated positive dynamics in disturbed functions recovery in comparison with the patients who received placebo, reaching a level of confidence (scores 9.1 and 5.6, respectively, $p < 0.05$) to the 11th day (Fig. 1). Considerably better recovery of neurological functions was observed in patients enrolled to the trial during the first 6 hours after the stroke symptoms onset and received cortexin (8.8 and 4.62 in comparison with the placebo group, respectively). No significant difference in the severity of the condition in both groups of patients admitted later, were observed. By the 28th day after the stroke onset the mortality in patients received cortexin, was 3.1% (1 patient) and 10% (3 patients) in the placebo group.

The aim of the study of Kurenkova et al. [22] was studying the efficiency of early rehabilitation measures in patients with IS with cortexin therapy providing neurometabolic protection of brain in the patients after stroke. The trial included 35 patients (21 men, 14 women) with hemispheric IS aged from 45 to 68 years. All patients were admitted to hospital during the first 24 - 48 hours after the onset of acute IS. General clinical examination was performed including somatic and neurological examination with the assessment by special scales of neurological symptoms severity (NIHSS score, modified Rankin scale, Rivermead mobility index). The patients were randomly divided into two groups: Group 1 (basic) - 19 persons; Group 2 (control) - 16 persons. All patients received basic IS therapy aimed at normalizing of homeostasis, central and cerebral hemodynamics. In addition to the basic therapy 19 of 35 patients received cortexin (10 mg i.m. within 10 days). By the time of enrollment to the trial the evidence of neurological deficit in both groups was virtually the same (NIHSS score 9-10, Rankin scale score 3-4, Rivermead mobility index 6-7). By the end of hospitalization (on the 15-16th day) NIHSS score in the basic group decreased from 9-10 to 2-5, Rankin score from 3-4 to 1-2, Rivermead mobility index Rivermid changed from 6 7 to 9-14. In the control group the neurological deficit varied much less.

The next found trial was performed in the clinic of nervous diseases of Kazakh National Medical University on the basis of neurorehabilitation department of the City clinical hospital N 1 [23]. The trial involved 68 patients at the early recovery period of IS aged from 45 to 74 years (average age 60,5 ± 2,8 years). The examined patients were divided into two clinical groups: the first group included 35 patients (51,5 ± 6,1%), the control group - 33 patients (48,5 ± 6,1%). Both groups of patients received basic therapy aimed at normalizing of disorders of systemic and cerebral hemodynamics, blood rheology, correcting of muscle tone and limbs movement. The patients of the main group received the basic therapy together with cortexin 10 mg i.m. previously dissolved in 2 ml of 0.9% isotonic sodium chloride solution. The duration of cortexin therapy was 10 days. The patients in the control group were comparable with the main group by age, sex, clinical and neurological manifestations of the early recovery period of IS and they received basic therapy. The criteria for efficiency evaluation were the recovery of disturbed neurological function and the condition of everyday adaptation by Orgogozo JM scale, the original scale, Barthel index. An increase of the total ischemic score was determined and it was just the same before therapy in both groups. By the results of the trial the recovery of disturbed functions in the patients in the early recovery period of IS who received cortexin was more significant in comparison with the control group.

All above trials of the efficiency of cortexin use at IS demonstrated a positive dynamics of the studied parameters: the results of clinical examination and instrumental studies, rating scales. However, as there is no data on statistically significant differences, the conclusions of the authors about positive dynamics of the studied parameters are probably unreasonable. Moreover, the disadvantages of the above trials are small sample size and short duration of the trial. When the trials is based on relatively small volume of sample, the results contain a significant uncertainty; it is unknown how the estimation of the therapy effect will change in future. In turn, a short period of observations does not allow making conclusions on long-term results. So according to the results of these trials the pharmacoeconomic research (PER) is unreasonable.

The trial of Stakhovskaya et al. [25, 26] included 272 patients with hemispheric IS, who were admitted to hospital in the first 24 hours after the symptoms onset. The trials lasted for 70 days. The patients of the Group 1 the cortexin was prescribed 10 mg twice daily for 10 days, with the same course repeating again after the break for 10 days. The patients in the Group 2 were prescribed cortexin 10 mg i.m. twice daily for the first 10 days, and after a 10 day break the active drug was replaced with placebo twice daily. The third group of patients received placebo in two courses of 10 days each, with a rate of administration, similar to the 1st and 2nd groups. The groups were the same by sex, age, severity of neurological deficit by NIHSS score at their admission. In this clinical trial the tests were carried out on the patients with moderate stroke (NIHSS score 7), which does not meet the aim of our PER.

Ceraxon (Citicoline)

Two publications with meta-analysis of citicoline use at IS were found.

J.L. Saver et al. published a formal meta-analysis of studies which included the results of 10 trials of citicoline in treatment of ischemic and hemorrhagic stroke. The purpose of this meta-analysis was to assess the positive therapeutic effect of citicoline. In 2279 patients enrolled in the study, the administration of citicoline was associated with a significant reduction of mortality or disability for a long follow-up period of in comparison with placebo (57.0 and 67.5%, odds ratio (OR) = 0, 64; 95% CI from 0.54 to 0.77;

p <0.001) [27]. This study does not meet the aim of our work because the studied patients had not only IS but a hemorrhagic too.

Meta-analysis performed by Dávalos A. et al. for 7 large US clinical trials, which were based on the evaluation of 1652 patients with acute IS and background neurologic deficit with NIHSS score ≥ 8 points, confirmed the efficiency of oral use of citicoline in doses of 500; 1000; 2000 mg/day for 6 weeks. The overall recovery of functions was achieved in 25.2% of patients who took citicoline in comparison with 20.2% of patients who received placebo. The most pronounced therapeutic effect was observed at taking the drug at a dose of 2000 mg/day: the overall recovery of functions was observed in 31.6% of patients with citicoline therapy and in 27.7% of those who took placebo (p = 0.0045). Citicoline therapy did not affect mortality within 3 months of follow-up (18.8% in patients who took citicoline and 17.8% in those who took placebo) [28]. This study included patients with NIHSS score 8 or more, so the study does not meet the aims of this PER.

In the revealed trial Warach S. et al., 2000 confirmed the neuroprotective effect of citicoline by changing the volume of irreversible destruction of brain tissue, which was evidently dose-dependent: if the focus size increased in average for 84,7% in placebo group, then it increased for 34% in patients who received citicoline in dose 0.5 g/day and for 1,8% in those who received dose 2.0 g/day [29]. The selected efficiency criterion in this trial is a surrogate point, which using is not expedient for PER.

In 2012 the results of the trial of A. Davalos et al. [30] were published and they revealed no differences between the groups of patients treated with citicoline and placebo by the criterion of "total recovery" and security. The study was terminated.

Parfenov et al. examined 24 patients with IS for efficiency and safety of ceraxon 2000 mg/day i.v. for 10 days, then orally for 35 days with evaluation of its impact on cognitive functions [34]. During the therapy period none of the patients died, no recurrent stroke, myocardial infarction or other vascular events were developed. The majority of patients (18 of 24) demonstrated gradual regression of neurological disorders, reduction of disability degree. Positive impact of ceraxon on cognitive functions was observed and their improvement to the 45th day after the disease onset. In this publication and in the trials of Martynov M. Yu. [32] and Nikonov V.V. [33] the test horizon was very short and the results were irrelevant.

Therefore none of the found studies of ceraxon use at IS is suitable for this PER.

Actovegin

No international randomized trials on the efficiency of actovegin at IS was found. However there is an experience of this drug use in the Russian Federation.

A comparative clinical trial of Vertkin et al. on actovegin and mexidol use was found. Assessment of t hospital stay duration did not reveal significant differences between the groups (actovegin group 27,4 ± 3,4 days and mexidol group 26,7 ± 2,9 days; p> 0.05). But assessment of stroke outcomes in actovegin group a reduction in mortality was observed. So at the therapy with actovegin it was 13.3% and in mexidol group it was 23.3% [35]. This trial did not indicate the characteristics of the studied patients, especially the IS severity level.

In the trial of Kozelkina et al. 2009 a comprehensive clinical and instrumental examination of 82 patients aged from 48 to 84 years with acute cerebral IS was performed [36]. In the trial an efficiency of combined neuroprotective therapy with ceraxon and actovegin was studied and according to the results of those studies the PER is unreasonable.

Cytoflavin

Two publications with the assessment of citoflavin efficiency at IS were found.

Fedina et al. showed in double-blind, multicenter trial with placebo control that use of citoflavin in 600 patients with stroke within a three-week period after the disease onset in basic therapy reduces mortality 2.3 times (7.6 vs. 17.3%) and that the average duration of hospital stay decreased from 28.2 to 23.5 days for placebo and citoflavin, respectively [37]. In this clinical trial the tests were carried out in patients with NIHSS score 11, which does not meet the aims of our PER.

The trial of Odinak et al. demonstrates the results of a multicenter study of cytoflavin efficiency in treatment of patients with acute IS [38]. The study included 70 patients (41 in the basic group, 29 in the control group). All patients were prescribed basic therapy for correcting systemic hemodynamics, rheological blood properties, preventing the stroke complications. The patients in the basic group received cytoflavin by the following scheme: drip i.v. infusion 20 ml (400 ml of 0.9% sodium chloride) twice daily from the 1st to the 10th day; orally 850 mg twice daily from the 11th to the 35th day. The dynamics of the disturbed functions recovery was assessed by NIHSS score, Rankin scale, Barthel Index. In result, a trend to more complete preservation of brain substance in acute stroke period was revealed at therapy with cytoflavin. Cytoflavin use contributed reducing the neurological deficit and increasing the ability of patients to self-care, which is associated with a smaller final volume of brain lesions. For this trial patients with IS with NIHSS score 9 were selected, that contradicts our search parameters.

Mexidol

Four clinical trials on the efficiency of mexidol use in patients with IS were found.

The trial of Skvortsova et al. included patients with IS aged from 45 to 85 years (51 persons) who were admitted received during the first 24 hours aft6er the disease onset [39]. Mexidol was administered at a dose 300 mg/day to 24 patients within 14 days after the stroke onset. The placebo was administered to 27 patients in a similar way. A significant outperformance in the regression of neurological disorders by NIH scale was revealed on the 14th day of the disease in patients treated with mexidol in comparison with the placebo group, and a significant functional recovery (dynamics of clinical Barthel score on the 21st day) was observed in patients enrolled to the trial within the first 6 hours after the disease onset. However, because of the short study horizon the obtained data are irrelevant and on this basis the PER is not possible.

In its trial Seregin V.I. [40] studied the neuroprotective efficiency of combined therapy with mexidol and gliatiline and on the basis on the results of that trail the PER is unreasonable.

In its trial Chefranova et al. [41] studied the efficiency of thrombolytic therapy at IS and its combination with mexidol. The results of that trial showed that the mexidol use in thrombolytic therapy at a dose of 500 mg daily for 21 days may reduce the size of the ischemic focus and increase duration of the therapeutic window, reduce the number of somatic complications. The exclusion criteria of the clinical trial from our selected publications are using of surrogate efficiency points, a short study period and the studied patients had a moderate severity level by NIHSS score (8-12).

The analysis of the trial performed by Shevchenko L.A. et al. [42] showed that the examined patients had different types of stroke (ischemic, hemorrhagic, subarachnoid, supratentorial), which was not the aim of our PER.

Cellex

No clinical trials of cellex use in IS therapy were found by February 2015.

Cerebrolysin

Data search revealed several clinical trials with participation of patients with IS.

The trial of Lang et al. [46] that was double-blind trial with placebo control included 119 patients with acute ischemic hemispheric stroke who were randomized for combined therapy with alteplaze/ cerebrolysin or alteplaze/ placebo (cerebrolysin and placebo were administered one hour after beginning of thrombolytic therapy with alteplaze) which was initiated within 3 hours after the onset of stroke symptoms. The daily intravenous infusions of cerebrolysin or placebo, both 30 ml, were performed for 10 consecutive days. The primary endpoint of the trial was the value of the modified Rankin scale on the 90th day of the trial. The third interim analysis showed no benefits of cerebrolysin before the placebo according to the data of modified Rankin scale on the 90th day of the trial, so the trial was terminated. The analysis of responders by NIHSS score (one of the secondary endpoints of the trial) showed a significantly greater number of patients with improvement for 6 or more points (or with the value of the total score 0 or 1) after 2, 5, 10 and 30 days in the cerebrolysin group. The similar trends were observed in the analysis of responders on the modified Rankin scale, although statistical significance was not achieved.

The results of Ladurner et al. [47] received in multicenter randomized controlled trial demonstrated that using of high drug doses (50 ml) significantly contributes to a more complete regression of neurological symptoms by the end of the acute period of the disease and improves the functional recovery and the restoration of self-help skills in the long period of stroke in comparison with placebo group.

The trial conducted by Skvortsova V.I. et al. [44], [45] demonstrated the ability of high doses (50 ml) of cerebrolysin to affect the dynamics of

morphometric focus picture in the brain of the patients with IS, which is manifested as reduction of the affected area size on MRI.

However, the greatest interest is referred to the results of a double-blind, randomized trial with placebo control involving 1070 patients (252 patients with NIHSS score > 12) [43]. The patients with acute IS were randomized within 12 hours after the onset of symptoms to receive active therapy (cerebrolysin 30 ml/day) or placebo (sodium chloride solution), which were administered by intravenous infusion for 10 days; the members of the trial also received aspirin (100 mg/day). The monitoring continued until the 90th day. Mortality was assessed in the subgroup with NIHSS score > 12. Total number of patients with baseline NIHSS score > 12 was 252. Among them 12 patients who received cerebrolysin and 22 who received placebo died. On the 90th day the cumulative percentage of died patients in the placebo group was 20.2% and in the cerebrolysin group 10.5% only. The analysis of life duration in the subgroup with baseline NIHSS score > 12 showed even more marked superiority of cerebrolysin (hazards ratio 1.9661; NGDI 1,0013; p = 0,02485). From the view of descriptive statistics this shows a statistically significant difference between the two groups and a significant advantage of cerebrolysin. This found trial meets all requirements of the set aim of PER.

Then publications containing non-standard indices or indicators that are not applicable to the aims of this study were excluded. On the basis of the results it was found that there are practically no works containing all interested indices. The detailed analysis showed that that only the work of Wolf-Dieter Heiss et al, 2012 contained the results by all parameters meeting the aims of this study [43].

Therefore the data search gave an opportunity to perform PER of treatment of the patients with acute moderate and severe IS with using cerebrolysin in comparison with the basic therapy.

Pharmacoeconomic modelling

To perform this PER an analytical decision-making model (ADMM) was developed. The model was built on the basis of retrospective data on the population of patients with moderate and severe IS, the structure and the efficiency of care and the direct and indirect costs for the patients therapy. Pharmacoeconomic analysis within ADMM can be performed as for the budget of the health system as a whole, including direct and indirect costs, or as for the budget of health care center (HCC), which takes into account only the direct costs [17, 18]. This article presents the modelling results as for the budget of the health system as a whole. The study was performed using the following methods: efficiency analysis, cost analysis, modelling, "cost-efficiency" analysis, "impact on the budget" analysis 'and sensitivity analysis.

Efficiency analysis

On the basis of data search the efficiency criteria were defined which allowed providing pharmacoeconomic evaluation of compared health technologies for moderate and severe IS therapy. LYG (life years gained) was such criterion in this PER. Data presented in the table 2 were obtained for the horizon period of the trial which equals one year and at the rate of treatment per one patient. We assumed that the efficiency specified in the clinical trial performed by Wolf-Dieter Heiss et al for the 90th day will not change during the year. The assumptions made at health care resources using were made for the case when there were no enough data from clinical trials. One more assumption connected with dose-dependent effect was made in our study. At the efficiency analysis the search of data of average duration of hospital stay was performed. This parameter was found in a clinical trial performed by Gusev E.I. et al., where it was revealed that the duration of hospital stay for the patients treated with cerebrolysin 20 ml/day was 26,3 ± 2,1 bed-days in average [48]. Taking into account that there exist clinical trials proving that the greater is the dose, the faster and the more pronounced is a therapeutic effect, we made an assumption that this efficiency criterion will be the same for the cerebrolysin 30 ml/day.

Table 2. Results of efficiency analysis for the compared treatment designs.

Efficiency criterion	Cerebrolysin + basic therapy	Basic therapy
LYG	0,9014	0,8132
Duration of hospital stay (days)	26,3	30

Costs analysis

In the course of this PER the costs per treatment of one patient with IS was calculated, considering the basic therapy and the basic therapy and cerebrolysin. The study considered both direct and indirect costs for IS treatment. The total value of costs consisted of direct and indirect costs. The direct costs included the costs of pharmacotherapy with cerebrolysin, the cost of ambulance call, the cost of diagnostics, treatment and drug therapy according to:

- the Order of the Ministry of Health of Russia N 1740 н of 29.12.2012 "On the approval of the standard for specialized care at brain infarction " [49]
- the Order of the Ministry of Health and Social Development of the Russian Federation N 534 of 22.08.2005 «On measures of improvement of neurorehabilitation care in the patients with stroke and traumatic brain injury" [50]
- the Order of the Ministry of Health and Social Development of the Russian Federation N 236 of 22.11.2004 «On approval of the standard of medical care in patients with stroke in out-patient care" [51]

The indirect costs included such costs as a loss of Gross Domestic Product (GDP) due to disability and mortality, the cost of disability, sick leave (SL) payments.

The horizon period for this study was one year. The values obtained for cost analysis are presented in the table 3.

Table 3. Results of the costs analysis for treatment of moderate and severe IS of one patient per year

	Cerebrolysin + basic therapy	Basic therapy
Cost of pharmacotherapy with cerebrolysin, rub.	14774	0
Emergency medical care, rub.	3795	4024
Medical care in the hospital, rub.	100998	122170
Early neurorehabilitation, rub.	34127	36190
Out-patient medical; care, rub.	5993	5826
Cost of disability, rub.	68519	77210
Loss in GDP due to disability and mortality, rub.	145573	208158
Sick leave payments, rub.	4498	4403
Total	378278	457981

The table 3 shows that the overall cost per one patient taking cerebrolysin with a basic therapy equaled 378278 rubles. For patients who received basic therapy only it was 457 981 rubles. According to these values and the costs analysis, it was concluded that therapy of moderate and severe IS with cerebrolysin and the basic therapy requires less costs in comparison with the basic therapy only. Saving takes place due to reduction of the indirect costs and this is associated with lower mortality when using cerebrolysin together with the basic therapy.

"Costs - efficiency" analysis

At the next stage of the study, on the basis of the results of costs analysis and the data revealed in the analysis of efficiency and demonstrating statistically significant differences in mortality of patients with moderate and severe IS, a "cost - efficiency" analysis was performed for the treatment rate per one patient. The coefficient "cost-efficiency" is defined by formula:

$$CER = \frac{Cost}{Ef}$$

where: CER – coefficient "costs - efficiency";
Cost – costs for medical technology, rub.;
Ef – efficiency factor of medical technology.

Therefore in this study the coefficients "costs - efficiency" were

determined when using cerebrolysin for therapy of moderate and severe IS in patients in comparison with the basic therapy. As it was noted, "life years gained" was taken as an efficiency criterion. The values of "cost-efficiency" coefficients are given in the table 4.

Table 4. Results of "cost-efficiency" with efficiency criterion "life years gained"

Parameter	Cerebrolysin + basic therapy	Basic therapy
Costs, rub.	378278	457981
LYG	0,9014	0,8132
«Costs - efficiency» coefficient	4197	5632

These results show that the least cost for a year of life gained is referred to the scheme with cerebrolysin. Therefore the basic therapy in combination with cerebrolysin is characterized by a lower "cost-efficiency" coefficient in comparison with the basic therapy and so it is a dominant technology as for the "cost-effectiveness" analysis.

«Budget impact» analysis

Then in this pharmacoeconomic modeling we analyzed the "budget impact" as for the health care system in general in therapy of moderate and severe IS in two scenarios - the current situation (Scenario 1) and the model situation (Scenario 2) of therapy design. These scenarios include the possibility of regulating of the part of patients with one or another therapy design and setting the number of patients in the model. We assumed that in the current situation 100% of patients received basic therapy, and in a model situation absolutely all the patients received cerebrolysin with basic therapy. The horizon period for the "budget impact" analysis was one year (table 5).

Table 5. The results of "budget impact" analysis for one statistically average patient per year

Scenarios	Therapy design	Patients	Costs, rub.
Current distribution	Cerebrolysin + basic therapy	0%	457981
	Basic therapy	100%	
Planned distribution	Cerebrolysin + basic therapy	100%	378278
	Basic therapy	0%	
Money saving			79703

So the results of "budget impact" analysis showed that when the patient is transferred from the basic therapy to the treatment with cerebrolysin + basic therapy, then the costs will be reduced by 79703 rubles.

Sensitivity analysis

Sensitivity analysis allows evaluating the reliability of the results obtained and the extent to which the results of the trial will change at the initial parameters changing. The cost of cerebrolysin was taken as variable parameter. The sensitivity analysis showed that when the cerebrolysin price changes for 30%, the results of "cost - efficiency" analysis remained stable.

Conclusions

At pharmacoeconomic analysis of treatment of patients with moderate and severe IS (NIHSS score > 12) it was established that:

1. Today cerebrolysin only has an evidence base for the treatment of patients with moderate and severe IS (NIHSS score > 12).
2. Analysis of the "Budget impact" analysis showed that when the patient is transferred from the basic therapy to the treatment with cerebrolysin + basic therapy, then saving will be equal 79703 rubles.
3. As for the analysis of "cost-effectiveness" a basic therapy in combination with cerebrolysin is a dominant technology for treatment of moderate and severe IS in comparison with the basic therapy.

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