

Our Research Regarding Neurorehabilitation Outcomes of The Treatment with Calf Blood Deproteinized Medicine (Actovegin®) in Subacute/Subchronic Stages of Ischemic Stroke Patients – Preliminary Results

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ABSTRACT

Background. In the central nervous system's diseases panel, stroke is mentioned as a leader in incidence as well as medical and economic matter causing to patients major long-term physical, emotional and cognitive disabilities. The medicine Actovegin® is considered to have many beneficial effects although scarcely studied in ischemic stroke.

Objectives. The aims of the study was to comparatively assess the outcomes (functional and biological) of Actovegin® therapy on post-ischemic stroke patients treated with this medicine versus patients who received only standard, supportive and neuro-rehabilitative therapy.

Material and method. This study is bicentric, deployed evaluating patients hospitalized in the Physical and Rehabilitation Medicine & Balneology Clinic Division – The NeuroRehabilitation Compartment, of the Teaching Emergency Hospital of the Ilfov County – and in the Neuromuscular Rehabilitation Clinic Division of the “Bagdasar-Arseni” Teaching Emergency Hospital, both in Bucharest, Romania, between November 2014 - March 2020, with the diagnosis of (subacute/ subchronic) ischemic stroke at their first admission (about 4 weeks duration/ length of stay), within 4 months since their first acute cerebro-vascular event. We enrolled, for now, 66 patients with ischemic stroke. The control group included 37 patients with only standard supportive and neuro-rehabilitative, therapies; the study group (29 patients) received, additionally, treatment with 2 vials of Actovegin® (400 mg) in 250 ml sodium chloride 0,9% i.v. infusion, one infusion daily, during the first 2 weeks, followed by 3 tablets Actovegin® (600 mg) daily, for another 2 weeks. Outcomes were objectified through the following scales: FIM total (t), FIM motor (m), FIM cognitive (c), mR(D)S, GOS, GOS-E, ADL, IADL, BI, MMSE – Folstein questionnaire, SS-QOL, AST and through standard

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biological parameters of the inflammatory syndrome (number of leukocytes, percentage of neutrophils, ESR, fibrinogenemia), all comparatively: at discharge versus admission.

Results. *The outcome specific scores showed for the Actovegin® group, compared to the control group, a superior mean in FIMt and FIMm, highly significant ($p < 0.001$) and in percentages, significantly on GOS 95% CI 27.28% to 68.34%; the number needed to treat – NNT – was 2.1 (between 1.5 and 3.7), and respectively on mR(D)S 95% CI 57.19% to 89.68% and NNT was 1.4 (between 1.1 and 1.7). There weren't observed statistically significant differences between discharge and admission, on FIMc and MMSE scales and respectively, on standard biological parameters of the inflammatory syndrome. It has been observed the highest level of mean efficiency of Actovegin® on the Barthel Index (med = 50%, m = 54%, SD = 26.11%) and the lowest one on the IADL (med = 11.8%, m = 12.39%, SD = 11.43%).*

Conclusion. *Actovegin® produces some measurable improvements in the clinical-functional evolution of subacute/subchronic ischemic stroke patients, especially on motor outcomes, emphasized by standardized scales.*

Keywords: Actovegin®, ischemic stroke, rehabilitative outcomes, clinical-functional standardized assessment instruments, biological parameters of the inflammatory syndrome

Abbreviations

CNS = central nervous system, QOL= quality of life, BBB = blood- brain barrier, IPOs = inositol-phospho-oligosaccharides, PARP = poly ADP ribose polymerase, MCA = middle cerebral artery, ACA = anterior cerebral artery, PCA = posterior cerebral artery, VA= vertebral artery, TBI = traumatic brain injury, SCI = spinal cord injury, FIM = functional independence measure, GOS = Glasgow outcome scale, GOS-E = Glasgow outcome scale-extended, mR(D)S = modified rankin (disability) Scale, ADL = (index of independence in) activities of daily living, IADL = instrumental activities of daily living scale, BI = Barthel index, MMSE = mni-mental-state examination (Folstein questionnaire), SS-QOL = stroke specific quality of life scale, AST= aphasia screening test (Whurr – adapted), ESR = erythrocytes sedimentation rate.

INTRODUCTION

The central nervous system (CNS) illness are major sources of burden to both patients and caregivers, that severely affect the quality of life of patients (1), entailing huge individual and community expenses, with tremendous family, social and labour implications, at the same time. Thus, in this panel diseases, stroke is mentioned as a leader in incidence, as well as a medical and economic matter (2).

Stroke has "gained" the second place on death causing diseases incidence in general worldwide mortality (1,3,4) and the third place in the USA general mortality (2). For the individuals affected, this disease causes significant physical, emotional and cognitive disabilities among survivors (2), around 75% of them remaining with various degrees of (not rarely life-long) disability after discharge (4,5). Therefore, stroke ranks highly among causes requiring long term care (1). Furthermore, stroke is a major worldwide public health issue no matter if are high, middle or low incoming countries, but there are significant differences, for instance, among Eastern and Western European countries. From this perspective, Romania held (in 2015) an unwanted leading position among the EU countries as numbers of stroke new cases and deaths by stroke, as well (4,6). This unfortunate reality gave us one of the reasons to make research in this field.

In the last decades, neuroprotective and/or neurotrophic medicines and related dietary supplements

are considered as some valuable therapeutic candidates in overall brain recovery after local/ regional multifactorial damages. Such molecules/compounds represent, nowadays and probably in the future, too, an important challenge for the scientists and physicians working in the field. Enhancing the quality of life (QOL) through the synergistic therapeutic action mode between these agents and physical rehabilitation methods is the most desired purpose in the neuro-rehabilitation current activity (1).

The calf blood deproteinised ultrafiltrate/hemodialysate – Actovegin® (Takeda Austria GmbH, Linz, Austria) is a helpful pharmacological neuro-bio-trophic compound with has beneficial actions including in ischemic stroke, but related published literature data are rather scarce (4). Actovegin® is a hemoderivative/hemodialysate made by calf blood through ultrafiltration, finally being obtained an antigens and proteins free bunch of over than 200 bioactive molecules with weights under 5 kDa (7-10), consequently with potential to pierce the blood-brain barrier (BBB) (11). The chromatography analyse pointed out a large spectrum of bio- compounds among which the main ones are inositol-phospho-oligosaccharides (IPOs) and many other substances (highlighted by decreasing concentration): hexose (38.5%), amino acids (25.8%), lactate (21.2%), vitamins (11%), biogenic amines (2.2%), acyl-carnitines (0.2%), free fatty acids (0.03%); it also contains succinate, polyamines, glycosphingolipids, eicosanoids, electrolytes (e.g. sodium, phosphate,

potassium, magnesium, chloride, calcium), choline, adenosine monophosphate (AMP) (7,9,11-13); because of these multiple-compounds, a unique bio-active molecule action within it it's not possible to trace (9).

The Actovegin® mode of action confutes the prior utopist idea about using neuroprotective molecule with only one mechanism of action (14) and being a pharmacological bundle of substances, has pleiotropic, neuroprotective, and metabolic effects, which thus also fits this future vision of an integrated treatment paradigm (7). Actovegin® may have beneficial interferences at the intimate levels with some of the main pathophysiological pathways of ischemic stroke (4), such as: diminishes the oxidative stress by counteracting the poly ADP ribose polymerase (PARP) activity (7,10), mitigates the inflammation by NK- κ B pathway counteracting, and also apoptosis processes, through reducing the caspase-3 activation by amyloid β -peptides (A β s) (7-9,11,15). It straightens the oxygen and glucose consumption and the energy production in brain tissues, too (16), supporting cells by protecting them of hypoxia and acidosis (8,17,18). Actovegin® has, at the same time, a beneficial role in glucose regulation through its main component (IPOs) by the action of glucose transporters (7,12), and having, this way, an insulin-like activity (18). It was also described in literature the neuroprotective effects of Actovegin® by enhancing the neurons and synapsis number (7).

All this bundle of favourable effects on stroke's pathophysiological cascades, induced us to investigate the clinical-functional and biological outcomes after this medicine's administration in ischemic stroke patients, as we have determined to be still rather poorly evaluated in the related literature.

OBJECTIVES

The *principal goal* of this work was to evaluate the influence of treatment with Actovegin® on post-ischemic (subacute/subchronic) stroke therapeutic-rehabilitative outcomes, by comparing (discharge vs. admission) the clinical-functional related results, during the first hospitalization, of about four weeks, in a neuro-muscular rehabilitation clinic division. The *secondary goal* was to appreciate the dynamics of the biological inflammatory syndrome, also by comparing the values of biological outcomes collected from blood, at admission and discharge after four weeks of hospitalization.

MATERIAL AND METHODS

This is a bicentric case-control study, mostly prospective, but also partially retrospective (see further),

unfolded in the Physical and Rehabilitation Medicine & Balneology Clinic Division – The NeuroRehabilitation Compartment, of the Teaching Emergency Hospital of the Ilfov County (TEHIC) and in the Neuromuscular Rehabilitation Clinic Division, of the "Bagdasar-Arseni" Teaching Emergency Hospital (TEHBA), both in Bucharest, Romania. In this purpose, there have been obtained the necessary approvals from the two above mentioned institutions' Ethics Commissions (No: 12403/21.11.2014 from the TEHIC and respectively No: 3090/21.11.2014 from the TEHBA) and all the enrolled patients received, read and signed the patient's Informed Consent (by themselves, by first degree relative or by the legal representative). So, during the investigations and data retrieval, there were respected the medical ethics principles and approaches, and anonymity of patients.

We have obtain also the approval of conducting the non-interventional clinical study from the national authority in the field: The Romanian Ministry of Health, respectively by The Medicines and Medical Devices National Agency (No: 38032/19.09.2016).

There were enrolled – and recorded data from – only patients being at their first admission (in one of the two above mentioned clinic divisions), between November 2014 and March 2020, with diagnosis of ischemic stroke in subacute/ subchronic stages, within the first 4, up to 16 weeks, since their first acute cerebral-vascular event. Specifically, we enrolled, for now, 66 patients with ischemic stroke (for partial results validation), divided into a control and respectively, a study, group/ lot. The control group included 37 patients, with only standard supportive and neuro-rehabilitative, therapies; the study group (29 patients) received, additionally, treatment with Actovegin®.

Inclusion criteria (for both groups): patients from both genders, 18 years old or more, suffering of the first ischemic stroke, of over 4 cm³ in subacute/ subchronic stage, in the territory of the: MCA/ACA/ PCA/VA, being at their first admission in a neuro-muscular rehabilitation clinic division, and who didn't receive any neuroprotective or neurotrophic, multimodal or pleiotropic, medicines, before or during the study evaluation (only for the study group).

Exclusion criteria (for both groups): patients with age under 18 years, with stroke's age over 4 months, lactation and/or pregnancy, severe co-morbidities (heart / pulmonary / kidney / liver failure), cancer, traumatic brain injury (TBI) or spinal cord injury (SCI) concomitance, orthopedic diseases with trunk and/or limbs trauma, severe CNS diseases (severe multiple sclerosis, severe dementia), patient's denial, patients who have received neuroprotective or neurotrophic, multimodal or pleiotropic, medicines, before or during the study evaluation (only for the study group).

RESULTS AND DISCUSSION

Baseline / admission assessments situation

The two patients groups (the study one – Actovegin® treated – and the control one) were homogeneous; this means at admission it was not a statistically significant difference between groups concerning the following parameters: gender ratio ($p = 0.136$ Fisher's exact test), age ($p = 0.850$ t test), demographic details (urban, rural) ($p = 0.292$ Fisher's exact test), hospitalization days number ($p = 0.053$ Mann-Whitney non-parametric test), leucocytes number ($p = 0.323$ Mann-Whitney test), neutrophils percent ($p = 0.842$ t test), ESR ($p = 0.160$ Mann-Whitney test), fibrinogenemia ($p = 0.106$ t test).

In the next stage of analysis, we have proceeded to comparatively assess the two groups' clinical-functional status at baseline/admission, by the using the scales (/subscales): FIMt, FIMm, FIMc, GOS, mR(D)s, MMSE. The mean values at admission did not show statistically significant differences between both groups in all FIM scales (/subscales): FIM t (mean in the control group = 53 and in the Actovegin® treated group = 47.9; $p = 0.368$ t test), FIM m (mean in the control group = 33.5 and in the Actovegin® treated group = 29.2; $p = 0.314$ t test), and respectively FIM c (mean in the control group = 19.5 and in the Actovegin® treated group = 18.7; $p = 0.726$ t test). In all FIM scales' baseline/admission data was observed the study group apparently initiated from a lower functional level compared to the control one. In both groups the FIM t, m, c values were not normally distributed, but Kolmogorov-Smirnov test did not permit to exclude the normality: FIMt ($p = 0.946$ for the control and $p = 0.898$ for the study group), FIMm ($p = 0.445$ for control group and $p = 0.476$ for the study group), FIMc ($p = 0.607$ for control group and $p = 0.752$ for the study group).

For the MMSE data there were observed severe deviations from the normality ($m = 17.6$ for the control group and respectively, $m = 17$ for the study group) with $p = 0.026$ by Kolmogorov-Smirnov test for control group (despite the fact that for the study group was normality); for that reason we have used the nonparametric Mann-Whitney test that has shown non-significant differences between groups at baseline/admission ($p = 0.790$).

For the two scales that consist of few items each (GOS, mR(D)s), the provided data cannot be comprehensively statistically evaluated unless they are not dichotomized in sub-groups (see below). Apparently the data obtained using these scales differed at baseline/admission in both groups, but not statistically significant (for the GOS $p = 0.228$ and for the mR(D)s $p = 0.205$ given by chi-square test).

In the control group were included 37 post ischemic stroke patients: 24 women and 13 men, aged between 44 and 88 years old (med = 70; $m = 69.1$; $SD = 9.886$). The both groups of patients received the necessary complex and adapted, concomitant, medical treatment for their disease status and co-morbidities, concordant with current guidelines and were also included in complex individual programs of physical and kinesiotherapy associated or not with orthotic procedures.

In the study group were recruited 29 post ischemic stroke patients: 13 women and 16 men, aged between 34 and 94 years old (med = 70; $m = 69.7$; Standard Deviation (SD) = 14.180), who have received, additionally, treatment with 2 vials of Actovegin® (400 mg) in 250 ml sodium chloride 0.9% i.v. infusion, one infusion daily, during the first 2 weeks, followed by 3 tablets Actovegin® (600 mg) daily, for another 2 weeks. This treatment was initiated from the first or the second day of admission. The number of days between the stroke onset and the initiation of treatment with Actovegin® varied between 8 and 120 days (med = 35; $m = 41.24$; $SD = 28.772$).

Both groups were evaluated at baseline (in the first or few days after admission) and at discharge. The patients were followed-up during a hospitalization period: $m \pm S.D. = 22.5 \pm 5.8$ days, med = 21 days – for the study group – and: $m \pm S.D. = 20.1 \pm 8.2$ days, med = 18 days, for the control group. To evaluate the functional outcomes in the most objective way, we used the following standardized, and largely used internationally, ten/twelve scales: FIM – total (t), and also split into: motor (m), cognitive (c), subscales (19), GOS (20,21), GOS-E (21,22), mR(D)s (23,24), ADL (25,26), IADL (27,28), Barthel Index (29,30), MMSE (31,32), SS-QOL (33), AST (34). Aiming to increase the statistical power we have added 20 patients, evaluated retrospectively, as a sub-group in the control-group – to who, there had performed only four/six standardized scales [FIM(m), FIM(c), FIM(t), mR(D)s, GOS, MMSE].

For the assessment of the biological inflammatory syndrome we have used common measuring blood/biochemical parameters (number of leukocytes, percent of neutrophils, erythrocyte sedimentation rate, fibrinogenemia), at admission and discharge, as well.

The statistical analysis was performed using SPSS version 16 and version 24 for Windows®, Microsoft Excel® 2007 and Epi Info® version 3.3.2. (from 2005). Data distribution was examined using the one-sample Kolmogorov-Smirnov test; it was considered (approximately) normal if $p > 0.05$. To compare differences in parametric data we used the t test, if parameter values had a normal distribution and the Mann-Whitney test if not. We also used Fisher's exact and chi square tests, to compare frequency data. Values of differences were considered significant if $p < 0.05$ (35,36).

Evolution of assessed items

Discharge analysis

To assess the functional benefits at discharge (vs. admission), we have calculated “discharge – admission” scores in all the above mentioned scales, with the mention that mR(D)S calculated values were noted with “-” because this is a scale with inverse trend quantification paradigms, i.e. the higher is the score, the more severe is the disability.

FIMt evolution

The normality analysis showed that FIMt evolution values can be accepted as normally distributed ($p = 0.686$ for the study group and $p = 0.882$ for the control group, by the Kolmogorov-Smirnov test), so the results were appropriate for parametric testing. The median increase in FIMt score values was higher in the Actovegin® treated group than in the control one: 73 vs. 60 and the mean value was 69.1 vs. 58.3, S.D. = 23.56, respectively 25.6. The difference between means was 10.9: statistically significant ($p = 0.041$, t test). The control group had also statistically significant functional benefit at discharge vs. admission (as to be expected). However, this was smaller compared to the study (Actovegin® treated) group (5.3 vs 21.2); both of these increases are highly statistically significant ($p < 0.001$, t test; 95% CI 9.6 to 32.8). This mentioned evolution of FIMt score for both groups are below, graphically represented, in Figure 1 and Figure 2.

The next step was to calculate the *effect size* of Actovegin®, which in scales with more items (i.e. FIMt, FIMm, FIMc, MMSE) represents the difference between the means of evolutions/ improvements of the study patients and the means of evolutions/ improvements of the control patients, related to a specific scale and the result is numeral. In the other way of speaking, the control group had an “usual” (as expected) clinical-functional improvement, but the treatment with Actovegin® (received by the study group) brought a supplementary improvement (see further). On the other hand, in scales with few items [i.e. GOS, mR(D)s] it is first necessary to stratify patients in two categories, namely in “improved”, respectively “not-improved” patients (for both the study group and control group). It was calculated the percentages of “improved” patients in each of the two groups and the *effect size* was the difference of these percentages in the study group vs. the control one. From these percentages it was determined the corresponding NNT(-number needed to treat).

The effect size of Actovegin® objectified on the FIMt scale was calculated taking into account the difference between the means: discharge (d)_FIMt – admission (a)_FIMt in the treated vs. the control group (i.e. $69.1 - 47.9 = 21.2$ vs. $58.3 - 53 = 5.3$); the Effect size in FIMt was $21.2 - 5.3 = 15.9$ units of scale (14,7% amplitude), with 95% CI 4.2 to 27.6.

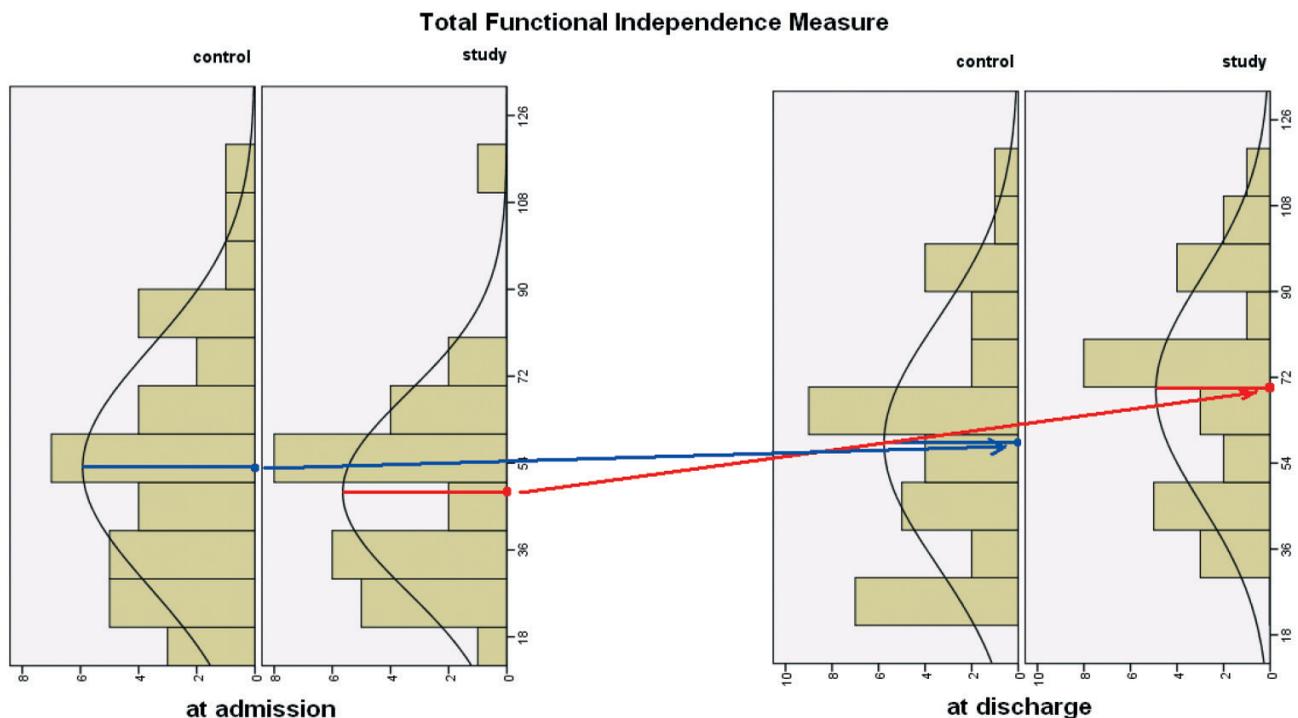


FIGURE 1. Evolution of FIMt scale in control and study groups (the mean values of FIMt at admission and at discharge for both groups: was 53 at admission, and respectively 58.3 at discharge for the controls; for the study group, was 47.9 at admission, and respectively 69.1 at discharge)

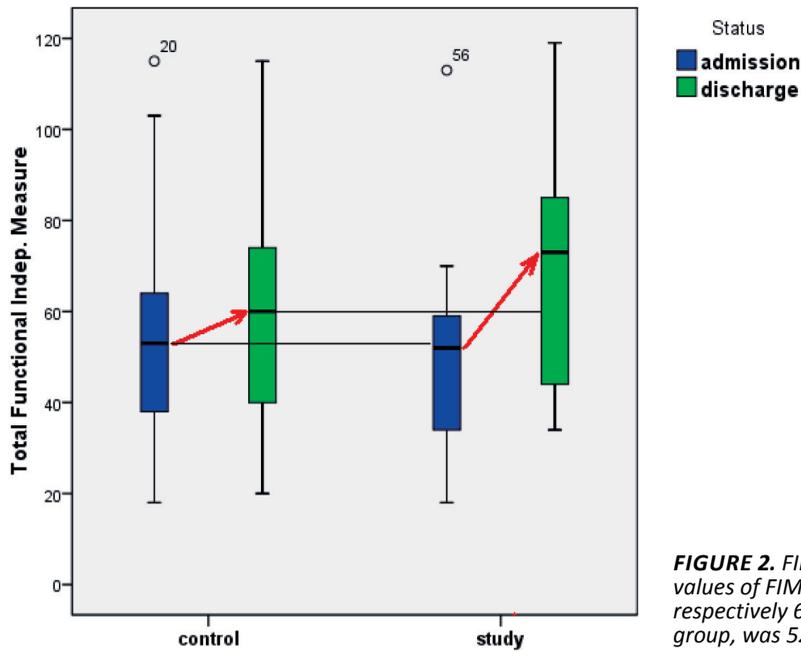


FIGURE 2. FIMt scale at admission and discharge (the median values of FIMt on both groups: was 53 at admission, and respectively 60 at discharge for the controls; for the study group, was 52 at admission, and respectively 73 at discharge)

FIMm evolution

The median increase in FIMm score values was higher in the Actovegin® treated group than in the control one: 43 vs. 35 (see in Figure 3) and the mean values were 47.2 vs. 38. The control group had statistically non-significant functional benefit at discharge vs. admission ($p = 0.304$, t test), but on the contrary, the study (Actovegin® treated) group had a high statistically significant clinical-functional improvement at discharge vs. admission ($p < 0.001$, t test) with 95% CI 8.3

to 27.6. The *effect size* of Actovegin® objectified on FIMm scale was 13.5 units of scale (17.3%), 95% CI 4.5 to 22.5. It represents the difference between the means: (d)_FIMm – (a)_FIMm in the treated vs. the control group.

FIMc evolution

The median increase in the FIMc score values was a little higher in the Actovegin® treated group than in the control one: 23 vs. 22 (see in Figure 4) and in the

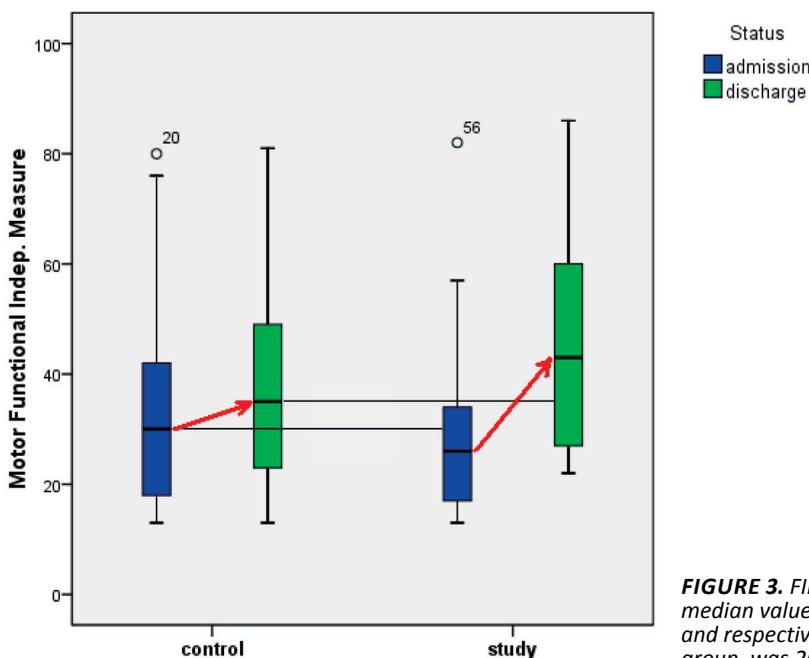


FIGURE 3. FIMm scale at admission and discharge (the median values of FIMm on both groups: was 30 at admission, and respectively 35 at discharge for the controls; for the study group, was 26 at admission, and respectively 43 at discharge)

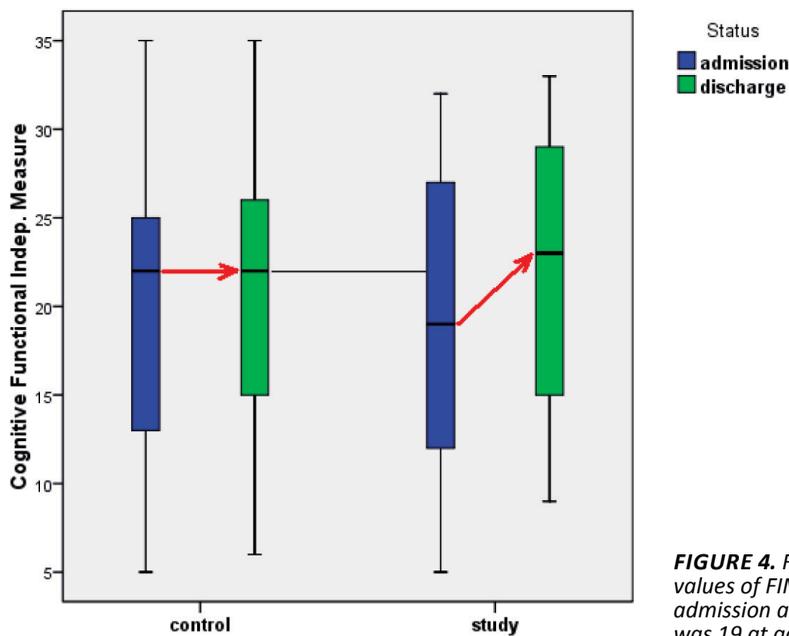


FIGURE 4. FIMc scale at admission and discharge (the median values of FIMc on both groups: was 22, the same value at admission and discharge for the controls; for the study group, was 19 at admission, and respectively 23 at discharge)

mean score value was a little higher, too: 21.9 vs. 20.3. The study (Actovegin® treated) group had a statistically non-significant functional improvement at discharge vs. admission ($p = 0.143$, t test) and so had the control group ($p = 0.695$, t test), but the study group improvement has higher (3.2 vs 0.8). The *effect size* on FIMc scale was only 2.4 units of scale (8 %), 95% CI between -1.8 and 6.6 (hence is statistically non-significant) and represents the difference between the means: (d)_FIMc – (a)_FIMc in the treated vs. the control group.

MMSE evolution

A quite similar evolution had the MMSE score values: the mean increase was very little higher in the Actovegin® treated group than in the control one: 18.3 vs. 17.9. Neither in the Actovegin® treated group nor in the control one any statistically significant benefit at discharge vs. admission has been observed ($p=0.654$ for the study group and respectively, $p=0.887$ for the control one – with t test). To compare the evolution of MMSE value in both groups, was used the non-parametric Wilcoxon test ($p = 0.066$ for controls – the great majority of the controls kept their admission values). The *Effect size* of Actovegin® on the MMSE scale was only 1 (3,3%), statistically non-significant.

GOS evolution

After dichotomization of both groups, each of them in two sub-groups – *improved*, respectively *not-improved* (as already described above) we could find the *effect size* as the difference between the percent of *improved* patients from the study group and the percent of improved patients from the control group. The

improved patients percentage was higher in the Actovegin® treated group vs. the controls (58.6 vs. 10.8). The *Effect size* was 47.8 percent, statistically significant, with 95% CI 27.28% to 68.34%; the NNT was 2.1 (between 1.5 and 3.7).

mR(D)s evolution

The improved patients percentage was higher in the study group comparatively to the control one (89.7 vs. 16.2). The *Effect size* was 73.5%, statistically significant, with 95% CI 57.19% to 89.68% and the NNT was 1.4 (between 1.1 and 1.7).

So, the Actovegin® 's *effect size* on the assessment scales above described, was highest on FIMt and FIMm and lowest on MMSE.

The next challenge was to calculate the *efficiency of treatment* with Actovegin®. This was calculated in the study group on all afore mentioned ten/twelve assessment scales, using the formula (for each related scale): $\text{efficiency of the treatment (\%)} = (\text{discharge Evaluation} - \text{admission Evaluation}) / (\text{maximum Evaluation} - \text{admission Evaluation, values})$

For the mR(D)s we used the following formula: $\text{efficiency of treatment (\%)} = (\text{admission mR(D)s} - \text{discharge mR(D)s}) / \text{admission mR(D)s}$.

We comparatively emphasize (see Table 1) the mean *efficiency* of the treatment with Actovegin® using the ten/twelve assessed scales' scores. It has been observed the highest level of mean efficiency of Actovegin® on the Barthel Index (med = 50%, m = 54%, SD = 26.11%) and the lowest one on the IADL (med = 11.8%, m = 12.39%, SD = 11.43%).

TABLE 1. Mean efficiencies of treatment with Actovegin (obviously, in the study group)

	Efficiency - Motor Functional Indep. Measure	Efficiency - Cognitive Functional Indep. Measure	Efficiency - Total Functional Indep. Measure	Efficiency - Glasgow Outcome Scale	Efficiency - Extended Glasgow Outcome Scale	Efficiency - Modified Rankin Scale	Efficiency - Index of Indep. in Activities of Daily Living	Efficiency - Instrum. Activities of Daily Living Scale	Efficiency - Mini Mental State Questionnaire	Efficiency - Barthel index	Efficiency - Whurr Aphasia Screening Test	Efficiency - Stroke Specific Quality of Life
Minimum	7.8	0	9	0	0	-25	0	0	0	15.8	0	3.3
Mean	32.78	22.28	29.79	41.38	18.91	20.23	44.48	12.39	14.22	54	22.76	27.3
Median	28	22.73	26.15	50	20	25	40	11.77	0	50	0	28.18
Maximum	76.9	50	64.3	100	40	33.3	100	43.8	75	100	100	62

Biological/ inflammatory parameters' evolution

Concerning the evolution of inflammatory syndrome, it wasn't observed statistically significant differences from discharge to admission on any of the assessed biological blood parameters (number of leukocytes, percentage of neutrophils, ESR, fibrinogenemia).

About safety profile, there were no side effects related to the administration of Actovegin® and none of the patients died or got worse during the observations. Epilepsy, a preexisting condition or a complication of stroke was a safe morbid frame, because as already known it is not among the contraindications of Actovegin® (37); 7 percent of the all study's patients had seizures background.

Study had some limitations, such as the small sample size (but these are only partial, preliminary results) and a relatively short period of follow up (on average 21 days). This might be an explanation for the cognitive improvement was not statistically significant, most of the related trials unfolding over a much longer observation period (months) (17). Larger patients groups are required to be used for more comprehensive related results.

As long as actually it doesn't yet exist a molecule or non-pharmacologic intervention able to cure the brain

after damages (38), we consider a gain every therapeutic approach which brings any improvement, including for post-ischemic stroke patient's clinical-functional evolution and consequent QOL.

CONCLUSIONS

Actovegin® is a safe treatment in subacute/subchronic ischemic stroke patients (including with that used dosage below its level mentioned in the leaflet) and produces some measurable improvements, even if not spectacular, in their evolution, especially on motor outcomes, objectified by assessments on standardized related scales. By its components, Actovegin® has capabilities to favorably influence also some concomitant diseases such as diabetes type 2 and cerebral or peripheral vascular disorders.

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