ORIGINAL ARTICLE

NEW APPROACHES REGARDING THE USE OF ACTOVEGIN® IN SUBACUTE/POSTACUTE/SUBCHRONIC TRAUMATIC BRAIN INJURY PATIENTS

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Manuscript received: January 2017

Abstract

Traumatic brain injuries (TBIs) are a major cause, including for significant disabilities, currently with no cure. The neurobiotrophic Actovegin® is considered, yet scarcely studied in TBI. The aim of the study was to comparatively assess the outcomes of Actovegin® therapy on post-TBI patients treated with this medicine *versus* patients who received standard therapy. The study was conducted on patients who were admitted for the first time to the Rehabilitation Medicine Clinic Division of The "Bagdasar-Arseni" Teaching Emergency Hospital, Bucharest, Romania, between December 2004 - May 2016, with the diagnosis of (post-acute) TBI at their first hospitalization (about 1 month duration), within 4 months since trauma. We reviewed medical records of 74 post TBI inpatients, admitted in our unit. The control group included 41 patients with only standard supportive and neuro-rehabilitative, therapies; the study group (33 patients) received additionally 200 mg Actovegin®, 2 tablets/day. Outcomes were objectified through the following scales: Functional Independence Measure (FIM - total (t), motor (m), cognitive (c)) modified Rankin (Disability) Score (mR(D)S), Glasgow Outcome Score (GOS), Disability Rating Scale (DRS), Activities of Daily Living (ADL), comparatively: at discharge *versus* admission. The evolution scores showed a mean increase in FIMt, FIMm, FIMc and respectively, DRS values, highly significant, for the Actovegin® group than for the control group ($p < 0.001$) and, in percentages, significantly higher on GOS ($p = 0.001$), mR(D)S ($p = 0.011$) and ADL ($p = 0.021$). Actovegin® administration appears to improve functional outcomes post TBI, measured on all the standardized scales we used. However, larger patients groups, prophensive including for adequate meta-analyses, are needed.

Rezumat

Traumatismul cerebral cranian (TCC) este o cauză majoră de dizabilități/invalidități semnificative, în prezent fără tratament curativ. Neurobiotroficul Actovegin® se consideră a avea unele acțiuni benefice (inclusiv) în astfel de cazuri - decomandată fiind însă mai puțin studiat in TCC. Scopul acestui studiu a fost evaluarea comparativă a tratamentului cu Actovegin® la pacienți cu status post TCC, tratați cu acest medicament *versus* un grup de pacienți care au primit terapie standard. Studiul a inclus pacienți aflați la prima lor internare (de aproximativ o lună) în Spitalul Clinic de Urgență „Bagdasar-Arseni", București, România, în perioada decembrie 2004 –mai 2016 și diagnosticați cu TCC (postacut), până la 4 luni de la traumă. Am analizat rapoartele medicale a 74 de pacienți cu status post TCC, internați în clinica noastră. Lotul martor a inclus 41 de pacienți doar cu suport terapeutic standard și de neurorecuperare; lotul de studiu a fost format din 33 de pacienți care au primit, în plus, Actovegin® 200 mg, 2 comprimate/zi. Rezultatele au fost evaluate prin următoarele scale: *Functional Independence Measure* (FIM – total (t), motor (m), cognitiv (c)), *modified Rankin (Disability) Score* (mR(D)S), *Glasgow Outcome Score* (GOS), *Disability Rating Scale* (DRS), *Activities of Daily Living* (ADL), comparativ la internare și la externare. Rezultatele obținute au arătat faptul că media valorilor scalelor FIMt, FIMm, FIMc și respectiv, DRS a fost semnificativ ameliorată în lotul de studiu (tratați cu Actovegin®) comparativ cu lotul martor ($p < 0.001$) și, în procente, semnificativ îmbunătățită, pentru GOS ($p = 0.001$), mR(D)S ($p = 0.011$) și ADL ($p = 0.021$). În concluzie, administrarea de Actoveginului pare să îmbunătățească rezultatele funcționale post TCC, măsurat prin toate scalele standardizate utilizate. Sunt necesare însă, grupuri mai mari de pacienți, pentru validarea acestor rezultate.

Keywords: Actovegin®, Activities of Daily Living scale (ADL), Disability Rating Scale (DRS), Functional Independence Measure (FIM), Glasgow Outcome Score Scale (GOS), modified Rankin Scale/Rankin Disability Score (mRDS), rehabilitation outcome, traumatic brain injury (TBI)

Introduction

Actovegin® is a highly purified (deproteinized) extract obtained from calf blood, and contains physiological components small enough (below 5000 Da) to cross the blood-brain barrier (BBB), being free of antigens or pyrogens. It contains more than 200 bio-active constituents [1-3], among which, very important are inositol phospho-oligosaccharides (IPOs) [2-4].

This drug has a multicomponent composition [1], therefore, separate constituent molecules effects within its complex mechanisms of action, could not be specifically pharmacokinetically/pharmacodynamically, traced [1, 2].

Aside a bundle of beneficial actions, there are also described some neural specific effects of Actovegin®, i.e. neuroprotective [4] and possible neuroregenerative (neuronal and excitatory synaptic contacts numbers) [1], providing tissues survival support in lesions (ischemic, thrombo-embolic, and/or excitotoxic [2]) within the central and peripheral nervous, systems [3] (CNS, PNS) including the reduction of the degeneration of peripheral neurons and the improvement of their functionality [5]. These actions might be due to its anti-oxidative [6] and anti-apoptotic properties [3], including anti-poly (ADP-ribose) polymerase (PARP) activation [7] and also to a beneficial interference with the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway (especially an anti-caspase-3 induced apoptosis, dose-dependent, when Aß fragments are present) [3, 6].

Hence, Actovegin® is used for almost 55 years [1, 3], including various neurologic conditions, such as TBI's [8], ischemic and haemorrhagic strokes [9, 10], cognitive impairments related to age and dementia, related behavioural conditions [10-13], diabetes mellitus including secondary polyneuropathy [4].

Since data on the use of Actovegin® in TBIs are still scarce, although some previous related favourable outcomes are reported in the literature suggesting this medicine does exert neuroprotective and neuro-regenerative effects, we investigated the clinical-functional results following its administration, in this type of pathology.

Materials and Methods

This is a case-control retrospective study, performed in the Physical (neural-muscular) and Rehabilitation Medicine Clinic Division of the "Bagdasar-Arseni" Teaching Emergency Hospital (BATEH), approved by the Bio-Ethics Commission of the institution (number 25824/19.12.2012).

The aim of this work was to assess the impact of Actovegin® therapy on post-TBI therapeutic-rehabilitative outcomes, by comparing the clinical functional evolution/results, during the first hospitalization, of about 1 month, framing within the mean hospitalization duration agreed by our National Social Health Insurance system, in our unit.

We reviewed the recorded data from patients that were admitted (for the first time) to our Clinic division between December 2004 and May 2016, with the diagnosis of TBI, in subacute/postacute/subchronic stages, within the first 4 months since the initial injury.

Inclusion criteria (for both groups): subacute/post-acute/subchronic TBI in adult patients, within 4 months of the initial injury; first admission to our Clinic division; Glasgow Coma Scale (GCS) 12 points or less (i.e. severe or moderate TBI); age ≥ 18 years.

Exclusion criteria (for both groups): patients with severe, life-threatening, co-morbidities: heart failure, lung failure renal failure, liver failure, cancer; lactation and pregnancy; stroke while TBI; more than 4 months from the initial injury; less than 15 days of hospitalization in our Clinic; admission to other medical departments previous to the admission in our Clinic division, except for: emergency units, intensive therapy care units, neurosurgery units, orthopaedic units; patients who received other drugs considered pleiotropic/multimodal (neuro-protective/-trophic/-synaptogenetic) nootropics: Cerebrolysin®, Alanerv®, Neurooptimiser®.

The study group included 33 patients: 7 women and 26 men, aged between 19 and 79 years old (M = 40.9 ± 15.6, Median = 40), encompassing TBI patients, who had received treatment with Actovegin®, 2 tablets (400 mg)/day for a period of around 1 month (M = 24.36 days). Actovegin® treatment was initiated within 24 - 48 hours from the admission.

The control group included 41 patients that did not receive Actovegin®: 3 women and 38 men, aged between 20 and 73 years old (M = 38.9 ± 15.5, Median = 37). In order to accurately discriminate the effects of Actovegin® therapy, the controls were selected to match the study group for baseline parameters (gender, age, initial functional scores – except for Disability Rating Scale), as well as for the number of hospitalization days (mean of the length of stay (LoS) for the study group = 28.72 days and for the control group = 27.9 days).

All patients within the two groups received the necessary and appropriate complex treatment for their conditions and co-morbidities, in accordance with current guidelines. Previous cranial surgical intervention, orthopaedic interventions, concomitant medication, and/or physio-/kinesiotherapy procedures (including those initially administrated, in supra-/acute stages, before admission to our ward) did not constitute an exclusion criteria.

Both groups were assessed at baseline and at discharge. The patients were followed-up during a mean period of 4 weeks: M ± S.D. = 28.7 ± 8.4 days, Median 30 days for the treated group and M ± S.D. = 27.9 ± 14.1 days, Median 23 days for the control group.

To objectively evaluate the functional outcomes, we used the following standardized, and validated scales: Functional Independence Measure (FIM – total (t), motor (m), cognitive (c)) [14], Glasgow Outcome Score (GOS) [15, 16], modified Rankin (Disability) Score (mR(D)S) [17-19], Activities of Daily Living (ADL) [20, 21], Disability Rating Scale (DRS) [22-25].

The statistical analysis was performed using SPSS 22.0 for Windows®, Microsoft Excel® 2013 and Epi Info® 7 version 3.5.4. Data distribution was examined using the one-sample Kolmogorov-Smirnov test; it was considered 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. Fisher's exact and chi-square tests were employed to compare non-parametric (frequency) data. Values of differences were considered significant if $p < 0.05$ [26, 27].

Results and Discussion

Admission analysis

As asserted above, the study (Actovegin® treated) and control groups were similar at baseline regarding the following parameters: Glasgow Coma Scale (GCS) 45 values ($p = 0.27$); neurosurgical interventions ($p = 0.051$); number of hospitalization days/LoS ($p = 0.76$, unpaired t test); use of sedative, hypnotic and neuroleptic drugs: benzodiazepines ($p = 0.653$), anticonvulsants/hypnotics ($p = 0.093$), miscellaneous antipsychotic agents ($p = 0.652$), anti-psychotics ($p = 0.131$); age groups under 45 (18 - 45) years old and over 45 years old ($p = 0.16$ chi-square test); demographic details (rural or urban) ($p = 0.22$ chi-square test); gender ratio ($p = 0.08$ Fisher's exact test), and therefore we could comparatively analyse them further, in an appropriate way.

The next step was to comparatively evaluate the two groups at admission/baseline by the scales we have used in this survey (FIMt, FIMm, FIMc, DRS, GOS, mR(D)s and ADL).

Neither for FIMt (mean admission score for the control group = 43.66, and for the Actovegin® group = 37.79, $p = 0.22$), nor for FIMm (mean admission score for the Control group = 31.44, and for the Actovegin® group = 26.21, $p = 0.180$), and respectively for the FIMc (M = 11.58 in the Actovegin® group and 12.22 in the Control group, $p = 0.649$) the mean values at admission did not show statistically significant differences between groups.

In the FIMt we observed that the control group started at baseline, apparently, from a higher functional (preserved) level compared to the Actovegin® group.

The FIM m and c values were normally distributed in both groups ($p > 0.05$, the Kolmogorov-Smirnov test), thus the FIMt values in both groups were also normally distributed; moreover, they had similar ranks ($p = 0.083$, the Mann-Whitney test).

We could determine, from the DRS mean scores analysis, that the two groups within the survey started from different scale values at baseline (M for the control group = 15.56, 95% C.I. 14.2 - 17.2, and for the Actovegin® group M = 18.91, 95%; C.I. 17.6 - 20.4, $p = 0.005$). Thereby, we could objectify that at baseline the patients of the study (Actovegin® treated) group, were overall in a statistically significant worse functional condition. To be noted that DRS (and mR(D)S) are scales with inverse trend paradigms, i.e. the higher the scores, the more severe the disability.

As for the GOS, mR(D)S and ADL assessment instruments, because they are scales encompassing, each of them, quite a few items, within statistical analysis, the data they produce cannot be assimilated to thorough quantitative information. Thus, we have used for the related comparative assay, the Median and respectively, the number needed to treat (NNT).

Consequently GOS scores differed significantly ($p = 0.19$) and both Medians had the value of 3; for mR(D)S scores it cannot be asserted that they differed significantly ($p = 0.2$), but their Medians where different (Median = 4 for controls and Median = 5 for the study group). This might indicate that the study (Actovegin® treated) group started at baseline from a worse functional condition; for ADL we cannot assert that admission scores differed significantly ($p = 0.24$) and both Medians had the value of 0.

Discharge analysis

In order to quantify the functional gain at discharge *vs.* admission, we defined the following parameters: using "discharge – admission" calculated scores, with the mention that DRS and mR(D)S calculated values were noted with "–".

FIM Total (FIMt) evolution

The normality analysis showed that FIMt evolution values cannot be accepted as normally distributed ($p = 0.2$ in both groups, Kolmogorov-Smirnov test), thus the results were not suitable for parametric testing. Instead, we used the nonparametric test Mann-Whitney.

The Median increase in FIMt score values was higher in the Actovegin® treated group than in the control one: 32 *vs.* 7 ($p < 0.001$, Mann-Whitney test; regarding the mean values, 30.64 *vs.* 10.61 S.D. = 20.51, respectively 9.61, 95% CI for mean 23.5 - 37.8; $p < 0.001$, respectively 95% CI 7.6 - 13.6; $p < 0.001$).

The control patients had also statistically significant functional gain at discharge *vs.* admission and we consider this is the normal evolution. At the same time, this was less statistically significant than that of the study (Actovegin® treated) group (Figure 1).

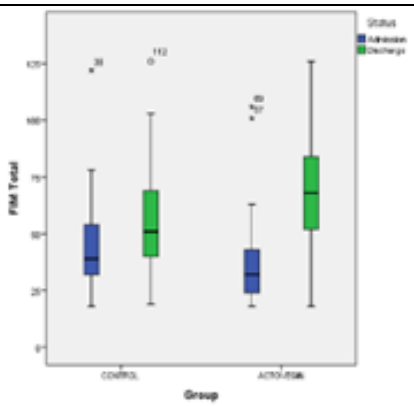

Figure 1.
FIMt at admission and discharge

To calculate the effect size, we used the efficiency formula [28]:

$$efficiency\% = \frac{discharge\ (FIMt) - admission\ (FIMt)}{126 - admission\ (FIMt)}$$

The effect size of Actovegin® (the difference between the means: d_FIMt – a_FIMt in the treated *vs.* control groups) was 22.8% (95% CI 21.7% - 24.1%).

FIMm evolution

The normality analysis showed that FIMm evolution values were approximately normally distributed (p = 0.104 in the control group and 0.536 in the Actovegin® group, the Kolmogorov-Smirnov test). Thus the results were suitable for parametric testing.

The mean increase in FIMm score values was higher in the Actovegin® treated group than in the controls: p < 0.001, t test, significant; regarding the mean values, 19.52 *vs.* 7.20, S.D. = 16.76, respectively 8.27, 95% CI for mean 13.6 - 25.4; p < 0.001, respectively 95% CI 4.61 - 9.78; p < 0.001.

The control patients had also statistically significant functional gain. At the same time, this was less statistically significant than that of the study (Actovegin® treated) group (Figure 2).

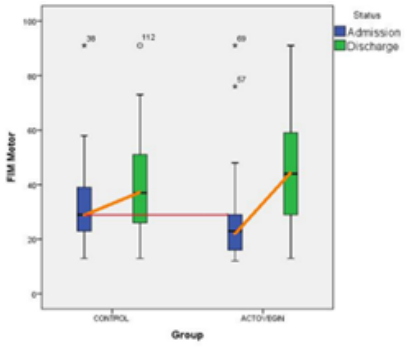

Figure 2.
FIMm at admission and discharge

To calculate the effect size of FIMm we used the efficiency formula:

$$efficiency\% = \frac{discharge\ (FIMm) - admission\ (FIMm)}{91 - admission\ (FIMm)}$$

The effect size of Actovegin® (the difference between the means: d_FIMm–a_FIMm in the treated *vs.* control groups) was 19.1%, (95% CI 18.1% - 20.3%).

FIMc evolution

The normality analysis showed that FIMc evolution/ functional gain values were approximately normally distributed (p = 0.299 in the control group and 0.416 in the Actovegin® group, the Kolmogorov-Smirnov test). Thus the results were suitable for parametric testing.

The mean increase in FIMc score values was higher in the Actovegin® treated group than in the control group: p < 0.001, t test significant; regarding the mean values, 10.94 *vs.* 3.41, S.D. = 6.01, respectively 2.91, 95% CI for mean 8.8 - 13.0, p < 0.001, respectively 95% CI 2.5 - 4.3, p < 0.001.

The parameters' values of the control group determined that these patients had also a statistically significant functional gain: discharge *vs.* admission and we can consider this is the normal evolution. At the same time, this was less statistically significantly compared to the study (Actovegin® treated) group (Figure 3).

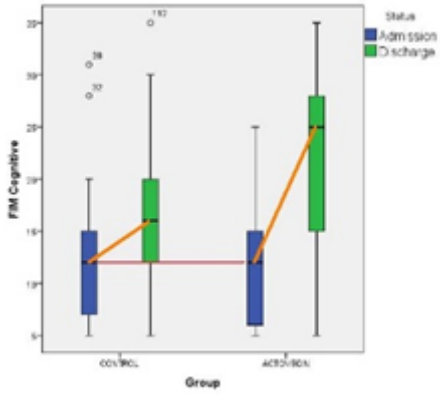

Figure 3.
FIMc at admission and discharge

To calculate the effect size of FIMc we used the efficiency formula:

$$efficiency\% = \frac{discharge\ (FIMc) - admission\ (FIMc)}{35 - admission\ (FIMc)}$$

The effect size of Actovegin® (the difference between the means: d_FIMc – a_FIMc in the treated *vs.* control groups) was 33.1%, (95% CI 31.9% - 34.4%).

DRS evolution

The normality analysis showed that DRS evolution values were approximately normally distributed (p = 0.098 in the control group and 0.306 in the Actovegin® group, the Kolmogorov-Smirnov test). Thus, the results are suitable for parametric testing.

The mean increase in DRS score values was higher in the Actovegin® treated group than in the control

group: $p < 0.001$, the t test significant; respectively the mean values, -7.27 *vs.* -1.71, S.D. = 3.83, respectively 1.71, 95% CI -5.87 - -8.33; $p < 0.001$, respectively 95% CI -1.13 - -2.28; $p < 0.001$.
We can consider that this is the normal evolution of the patients and determined that the control patients had also a statistically significant functional gain but this was statistically significant smaller than that of the study group (Figure 4).

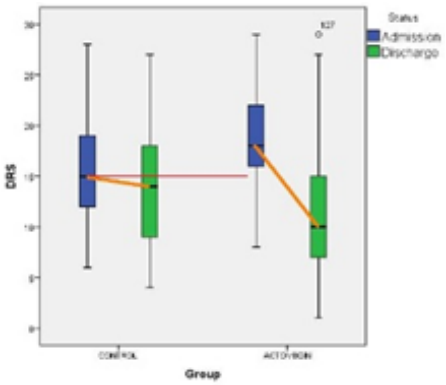

Figure 4.
DRS at admission and discharge

According to the evaluation on the DRS scale, the study (Actovegin®) group started/at baseline from a significantly worse overall status and this allows us to consider that the functional gain added by Actovegin® has an important clinical relevance.
Thus, we have chosen to proceed the comparative evaluation of the functional evolution between the two groups, using the efficiency formula:

$$efficiency\% = \frac{discharge\ (DRS) - admission\ (DRS)}{0 - admission\ (DRS)}$$

Accordingly, the mean efficiency was 12.7% in the control group and 41.4% in the Actovegin® group, with an effect size of the Actovegin® treatment of 28.7% increase in the mean efficiency (95% CI 19.8% - 37.6, $p < 0.001$). Consequently we can consider that Actovegin® treatment yields better results than standard therapy alone.
Since the GOS, mR(D)S and ADL, scores, are categorical, ordinal variables, to assess their evolution we have stratified them, by a customized formula by splitting the results of the scales in: "improved" (efficient) and "not improved" (inefficient). Thus, we could calculate the frequency (percentage of not improved/"bad" cases) in both groups and further, we could determine the related effect sizes and NNT according to the formula: effect size% = frequency of not improved cases in the control group - frequency of not improved cases in the study (Actovegin® treated) group.
Actovegin® treatment increased ("improved") the GOS scores percentualy, from 36.6% to 72.7% (chi-square test $p = 0.002$ and Z test $p = 0.001$). Compared to the control group the results were significantly higher: effect size = 36.1%, NNT (100%/ effect size%) = 2.77, 95% CI 13.26% - 59.03%).
Actovegin® treatment increased ("improved") the mR(D)S scores percentually, from 46.3% to 72.7% (chi-square test: $p = 0.022$; Z test: $p = 0.011$). Compared to the control group the results were significantly higher: effect size = 26.4%, NNT = 3.79, 95% C.I. between 3.7% and 49.0%).
Actovegin® treatment increased ("improved") the ADL scores from 53.7% to 78.8% (chi-square test: $p = 0.024$; Fisher's exact test: $p = 0.021$) and significantly higher compared to the control group: effect size = 25.1%, NNT = 3.98, 95% CI 3.2% and 47.0%.
Regarding the safety considerations, none of the patients died during the observation interval and there were no side effects related to the use of Actovegin®.
Findings similar to ours, regarding the effects of Actovegin® were described in a small clinical study, conducted on patients with mild and moderate TBI, in comparison to standard therapy [2, 8, 9, 11, 13].
Our study had some limitations, such as the small sample size and a relatively short period of follow-up (on average 4 weeks).
As afore emphasized, concomitant medication and/or physio-/kinesiotherapy procedures might have introduced a bias. The sedative, hypnotic and neuroleptic drugs could have interfered to some extent with the patients' baseline functional level and/or with the related outcomes. But since these drugs had to be used similarly in both groups, we consider this represented an objectively necessary, acceptable, limitation of the survey, that did not significantly impede the objective determination of the Actovegin® treatment's results, concerning whether it might have made a difference.
Given that the natural evolution of post-TBI disorders is a slow one, many TBI patients become "hyper-chronic" patients [29], developing over time, a wide array of complications and sequelae, therefore receiving further hospitalizations and/or ambulatory treatments in various medical settings. Monitoring the exact treatment doses and durations and tracking the effects of Actovegin® among the many (changed/ added) other therapeutic endeavours, over longer periods – with, inevitably, more new interactions – would be very difficult and probably distorted.

Conclusions

As resulting from our study, Actovegin® is safe (also for fidgety and/or epileptic cases) in subacute/sub-chronic (including with its ease of administration oral formulation) use at post TBI patients and produce some quantifiable improvements in their evolution,

as objectified by all of the standardized scales used in our study.

Moreover, the compound has the advantage of targeting some comorbidities rather frequently encountered in neurorehabilitation practice, such as diabetes mellitus and vascular disorders, according to its common (rather large spectrum) of therapeutic indications.

Disclosure

The producers of Actovegin® (Nycomed/Takeda) are constant partners of our societies (the Romanian Society for NeuroRehabilitation and the Romanian Spinal Cord Society) and Clinic Division. They did not interfere with this study (data collection or processing, concluding results or editing endeavours).

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