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Original article

COMPARATIVE EVALUATION OF REHABILITATION AND ACTOVEGIN TREATMENT VERSUS REHABILITATION TREATMENT IN PAINFUL DIABETIC NON INSULIN-DEPENDENT NEUROPATHY

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Abstract*

Aim: To compare the efficacy of Actovegin combined with rehabilitation versus rehabilitation in painful diabetic neuropathy (PDN).

Methods: In this observational trial, 28 patients received actovegin orally (divided in four groups, each group has 7 patients), first group rehabilitation without actovegin, second received 3 tablets of actovegin (1 tablet morning, 1 tablet afternoon and 1 tablet evening) combined with rehabilitation ,third group 6 tablets of actovegin (2 tablet morning,2 tablet afternoon and 2 tablet evening) combined with rehabilitation, fourth group 9 tablets of actovegin (3 tablet morning,3 tablet afternoon and 3 tablet evening) combined with rehabilitation.

Results: The study was conducted between January 2015 and June 2015 and shows the results of drug therapy versus rehabilitation for painful diabetic non insulin-dependent neuropathy after 6 months. Actovegin combined with rehabilitation are compared with rehabilitation for their efficiency and also the global perception of change by the patients. Patients were not allowed any other pain medication.

Conclusions: The study shows how the combination between actovegin and rehabilitation procedure are more efficiency than the rehabilitation alone, that suggest a neuroprotective activity of the drug.

Keywords: actovegin, rehabilitation, neuropathy

Introduction

Diabetic distal symmetric polyneuropathy (DPN) affects approximately one-third of diabetic patients and is associated with substantial morbidity including excruciating neuropathic pain and foot ulcers leading to amputation (Ziegler et al., 2008; Boulton et al., 2005).

Analgesics are effective in the treatment of neuropathic pain (Dworkin et al., 2007), but do not slow down the progression of the underlying neuropathy (Boulton et al., 2005). Various therapeutic approaches to treat DPN have been developed (Cameron et al., 1998), which address the pathology of the disorder, rather than just relieve pain (Ziegler et al., 1995; Boulton et al. 2005; Chalk et al., 2007). However, despite apparent recent progress, a potent sustainable therapy of DPN still remains an unsolved medical need.

Actovegin, a deproteinized hemodialysate produced from calf blood, containing low molecular weight compounds of up to 5,000 Da, has been shown to have substantial therapeutic benefits in DPN. Recently, a randomized, double-blind, placebo-controlled clinical trial with sequential intravenous and oral actovegin treatment of 567 patients with DPN was conducted over a period of 160 days (Ziegler et al., 2009). Actovegin treatment significantly improved neuropathic symptoms like vibration perception threshold, sensory function and quality of life of the DPN patients. The hemodialysate is approved as a drug (Actovegin®) in a number of countries and is applied to treat diabetic polyneuropathy and other diseases (for review see: Buchmayer et al., 2011). The protective effects of actovegin observed in the in vitro model may in concert contribute to the therapeutic benefits of the drug actovegin, which was observed in a clinical trial (Ziegler et al., 2009). In the respective randomized, double-blind, placebo-controlled clinical trial, it was recently shown that sequential parenteral and oral treatment with actovegin was associated with a positive effect on neuropathic symptoms, vibration perception threshold, sensory nerve function and mental health-related quality of life in patients with type 2 diabetes and symptomatic polyneuropathy. The results of the clinical study (Ziegler et al., 2009) are in line with the data obtained in vitro presented herein. The increased survival and synaptic density of neurons cultured in vitro in the presence of Actovegin suggest that protection and enhanced maintenance of neuronal networks may occur under conditions such as diabetic polyneuropathy or following trauma and stroke.

Earlier studies with a rat model of diabetic polyneuropathy, showed a reduction in intraepidermal nerve fiber density in skin biopsies, as well as a decrease in the loss of intraepidermal innervation upon therapeutic interventions (Bianchi et al., 2004). Here, the cellular effects of increasing

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doses of the hemodialysate actovegin were assessed in a neuronal in vitro model, namely in cultures of dissociated hippocampal neurons from embryonic rat brains. Cultured embryonic rat neurons constitute an accepted and relevant model system in the scientific community and have been widely used to evaluate the effects of pharmacologic and genetic interventions. Moreover, well-described culturing protocols and procedures for phenotypic characterization of cultures of embryonal rat neurons exist (Araujo et al., 2004; Burkarth et al., 2007; Cambon et al., 2004; Maar et al., 1997; Neiiendam et al., 2004; Skibo et al., 2005; Walicke et al., 1986). The following morphometric parameters were measured: the number of viable neurons, neurite outgrowth and synaptic connectivity. In parallel experiments, we assessed the anti-apoptotic effect of actovegin by measuring the levels of caspase-3 in response to amyloid peptide ($A\beta_{25-35}$).

Methods

Our objective was to compare the efficacy of Actovegin combined with rehabilitation versus rehabilitation in painful diabetic neuropathy (PDN).
In this observational trial, 28 patients received actovegin orally (divided in four groups, each group has 7 patients), first group rehabilitation without actovegin, second received 3 tablets of actovegin (1 tablet morning, 1 tablet afternoon and 1 tablet evening) combined with rehabilitation ,third group 6 tablets of actovegin (2 tablet morning,2 tablet afternoon and 2 tablet evening) combined with rehabilitation, fourth group 9 tablets of actovegin (3 tablet morning,3 tablet afternoon and 3 tablet evening) combined with rehabilitation. Pain relief was measured by the patient's global assessment of efficacy, using a visual analogue scale (0–10). Treatment goals include restoring function and improving pain control. Patients were randomly selected, the common factor being the presence of PDN. Patients of either sex with type 2 diabetes, aged between 25 and 83 years, who were on stable glucose-lowering medications during the preceding 3 month and who had PDN for at least 1 month were begin to be treated. Patients who had a pain score of >5, as assessed by visual analogue scale (VAS), were enrolled in our observation.

PDN was confirmed by 1) the patient's medical history, 2) a diabetic neuropathy symptom and increased thresholds on the vibration perception test and monofilament test. Patients were excluded if they had any clinically significant or unstable medical or psychiatric illnesses. Patients with other causes of neuropathy; renal dysfunction , liver disease; psychiatric illness; uncontrolled hypertension; those taking anticonvulsants, antidepressants, local anaesthetics, or opioids; those who were pregnant; lactating women; or those being treated with any investigational drug within the last 30 days were excluded from this observation.

First three groups underwent 6 months of treatment, at the end of 6 months, patients underwent clinical evaluation.

The primary end point of the study was the reduction of the average pain score from initial results, as assessed by the patient's global assessment of efficacy by the VAS (0–10 points). Secondary end points included the 24-point Hamilton Rating Scale for Depression; and patient self-evaluation of overall change on the basis of patient global impression of change scale.

Results

The study was conducted between January 2015 and June 2015.

Population and samples: Total population was 28 participants randomly selected, divided into 4 groups of 7. Age varies between 25 and 83 years old, mean age 53.42 (SD 15.75), 12 male patients and 16 female patients, with duration of diabetes between 3 and 17 years, mean duration 3.90 (SD 11.03).

Gathered data analysis

Table 1. Values reported on visual analogue scale (VAS) by patients measuring pain.

	First Group		Second Group		Third Group		Fourth Group	
	Before actovegin and reghabilitation procedure	Before actovegin and reghabilitation procedure	Before actovegin and reghabilitation procedure	Before actovegin and reghabilitation procedure	Before actovegin and reghabilitation procedure	Before actovegin and reghabilitation procedure	Before reghabilitation procedure	After reghabilitation procedure
Patient 1	5	3	6	5	9	5	8	2
Patient 2	6	5	7	6	8	2	9	1
Patient 3	5	3	8	6	7	1	10	3
Patient 4	7	7	5	5	6	3	8	3
Patient 5	6	6	9	8	7	5	7	2
Patient 6	9	8	8	7	9	5	9	1
Patient 7	8	8	7	6	10	3	10	4

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All data collections in above table have been tested for normality of distribution using Shapiro-Wilk normal distribution test, and Normal Q-Q Plots. All data collections have been found to have normal distribution.

Mean reduction of pain on VAS was calculated for each of the four groups and found a 13.08% improvement in the first group, 14% improvement in second group, 57.25% improvement in third group and 73.83% improvement in fourth group. Differences between mean values of pain on VAS for each group were tested with t-test for paired samples and were found statistically significant and non-accidental. We based differences found on medication treatment for the past six months. Also, using same test there were no statistically significant differences found between results of first and second groups, and not even between third and fourth groups, meaning that first groups showed similar efficiency with second groups and third showed similar efficiency with fourth group. Differences were however statistically significant between first (single rehabilitation) and third or fourth group and also between second group (3 tablets of actovegin and rehabilitation) and third or fourth groups (6 or 9 tablets of actovegin and rehabilitation).

Table 2. Depression scores on Hamilton Scale

	First group		**Second Group**		**Third Group**		**Fourth Group**	
Hamilton Scale Score	initial visit	after 6 months	initial visit	after 6 months	initial visit	after 6 months	initial visit	after 6 months
Patient 1	11	4	10	6	10	4	11	5
Patient 2	13	4	9	8	12	4	10	4
Patient 3	12	4	10	9	13	5	11	6
Patient 4	12	4	11	10	15	4	12	4
Patient 5	10	4	8	7	9	4	9	4
Patient 6	10	4	8	7	8	5	8	4
Patient 7	10	4	10	5	11	5	10	5

Initial assessment showed normal distribution of scores. The 6 moths visit showed statistically significant reduction of depression score for all patients.

Table 3. Overall perception of change

	First Group		**Second Group**		**Third Group**		**Fourth Group**	
Overall change	initial visit	after 6 months	initial visit	after 6 months	initial visit	after 6 months	initial visit	after 6 months
Patient 1	1	2	1	2	1	4	1	5
Patient 2	2	3	1	3	2	5	2	5
Patient 3	1	2	1	2	1	4	1	5
Patient 4	1	3	1	2	1	5	1	5
Patient 5	1	2	1	3	1	5	1	5
Patient 6	1	2	1	2	1	5	1	5
Patient 7	1	2	1	2	1	5	1	5

Overall perception of change, being a patient self-reported measure, like the VAS, showed similar results as the VAS after data analysis.

Discussion

Earlier studies with a rat model of diabetic polyneuropathy, showed a reduction in intraepidermal nerve fiber density in skin biopsies, as well as a decrease in the loss of intraepidermal innervation upon therapeutic interventions (Bianchi et al., 2004). Here, the cellular effects of increasing doses of the hemodialysate actovegin were assessed in a neuronal in vitro model, namely in cultures of dissociated hippocampal neurons from embryonic

rat brains. Cultured embryonic rat neurons constitute an accepted and relevant model system in the scientific community and have been widely used to evaluate the effects of pharmacologic and genetic interventions. Moreover, well-described culturing protocols and procedures for phenotypic characterization of cultures of embryonal rat neurons exist (Araujo et al., 2004; Burkarth et al., 2007; Cambon et al., 2004; Maar et al., 1997; Neiiendam et al., 2004; Skibo et al., 2005; Walicke et al., 1986). The following morphometric parameters were measured: the number of viable neurons, neurite outgrowth and synaptic connectivity. In parallel experiments, we assessed the anti-apoptotic effect of actovegin by measuring the levels of caspase-3 in response to amyloid peptide ($A\beta_{25–35}$).

There are numerous studies that compare different drugs in painful diabetic neuropathy (Bansal D, et al., 2009, Goldstein DJ, et al., 2005, Morello CM, et al., 1999, Wernicke JF, et al., 2007) but our study tries to make a comparison between actovegin plus rehabilitation procedure in painful diabetic neuropathy.

Conclusions

The current study compared the efficacy of combined actovegin (in different doses) and rehabilitation procedure compared with rehabilitation procedures in patients with PDN. All groups demonstrated comparable efficacy as per the established pain-rating scales for PDN. Numerically, more patients have pain relief after fourth and third over rehabilitation alone and second group (3 tablets of actovegin and rehabilitation) that suggest a neuroprotective activity of the drug.

In the present observational study, 6 tablets of actovegin with rehabilitation procedures 6 tablets of actovegin with rehabilitation procedures have similar efficacy and more than 3 tablets of actovegin with rehabilitation procedures and rehabilitation alone. More than 73% improvement in pain score was observed with fourth group and 57% with third group. Improvement in pain was significant and as a result, a significant reduction in depression scores was also observed. The overall self evaluation of patients is consistent with this result.

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