ORIGINAL ARTICLE

UDC: 615.03::[616.8-009.-02:616.379-008.64
https://doi.org/10.2298/VSP151209261C

Neurophysiological evaluation of short-term outcome of pharmacological treatment of diabetic neuropathy

Neurofiziološka procena kratkoročnog ishoda farmakološkog lečenja dijabetesne neuropatije

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Abstract

Background/Aim. Diabetic polyneuropathy (DPN) is a very frequent and progressive disease that severely impairs the overall quality of life, accompanied by a high rate of disability. For these reasons, the testing of therapeutic agents for this disease is increasing. **Methods.** We tested the most frequently used drugs for diabetic neuropathy in our area, along with electrophysiological monitoring in order to avoid subjectivity and the "placebo effect". A total of 120 patients were divided into four groups: three groups who received alpha-lipoic acid, benfotiamine or gabapentin respectively, and the control group who did not receive any treatment. In all the patients we analyzed motor conduction velocity, distal latency, sensory conduction velocity, F wave and F wave chronodispersion before and after treatment with each drug. **Results.** It is evident that some drugs had a favorable impact on the condition of the peripheral nerves. Alpha-lipoic acid and benfotiamine had an impact on the recovery of the nerve, i.e. pathophysiological processes, whereas gabapentin had no impact on the recovery, similarly to the control group without any treatment. Electrophysiological indicators had different sensitivity to detect conditions of the peripheral neurons. The best effect, in terms of increased sensory conduction velocity, had the patients treated with alpha-lipoic acid. **Conclusion.** The effect of alpha-lipoic acid and benfotiamine on the condition of peripheral nerve was evident. The failure of recovery, i.e. deterioration of electrophysiological parameters in patients who did not receive neuroprotective therapy suggests the need of permanent medication and periodic electrophysiological monitoring of patients with diabetic polyneuropathy.

Keywords:
diabetic neuropathies; electromyography; drug therapy; thioctic acid; thiamine monophosphate; gabapentin; treatment outcome.

Apstrakt

Uvod/Cilj. Dijabetesna polineuropatija (DPN) je veoma česta, progredijentna bolest koja dovodi do grubog urušavanja kvaliteta života praćenog visokom stopom invalidnosti. Iz tih razloga ispitivanje terapijskih sredstava za ovu bolest je u zamahu. **Metode.** Ispitivani su najčešće korišćeni lekovi za dijabetesnu neuropatiju u našem podneblju, uz elektrofiziološko praćenje da bi se izbegla subjektivnost i „placebo efekat“. Kod ukupno 120 bolesnika podeljenih u četiri grupe ispitivana je alfa lipoinska kiselina, benfotiamin i gabapentin, s tim što je elektrofiziološki praćena i grupa bolesnika koji u posmatranom periodu nisu dobijali terapiju. Analizirali smo motornu brzinu provođenja, distalnu latencu, senzitivnu brzinu provođenja, F talas i hronodisperziju F talasa, pre i posle terapije za svako pojedinačno terapijsko sredstvo. **Rezultati.** Evidentno je da su neki lekovi imali povoljan uticaj na stanje perifernog nerva. Alfa lipoinska kiselina i benfotiamini su imali uticaja na oporavak nerva odnosno patofiziološke procese, gabapentin je bio bez uticaja na oporavak, a slično je bilo i kod kontrolne grupe koja je bila bez bilo kakve terapije. Elektrofiziološki pokazatelji su imali različitu osetljivost na detekciju stanja perifernog neurona. Najbolji efekat koji se ogleda u povećanju senzitivne brzine provođenja imali su bolesnici koji su tretirani alfalipoičnom kiselinom. **Zaključak.** Uticaj alfa lipoinske kiselina i benfotiamina na stanje perifernog nerva je evidentno. Odsustvo oporavka, odnosno pogoršanje elektrofizioloških pokazatelja kod ispitanika koji nisu dobijali neuroprotektivnu terapiju, ukazuje na potrebu permanentne medikacije i periodičnog elektrofiziološkog praćenja bolesnika sa dijabetesnom polineuropatijom.

Ključne reči:
dijabetesne neuropatije; elektromiografija; lečenje lekovima; tioktinska kiselina; tiamin monofosfat; gabapentin; lečenje, ishod.

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Introduction

Diabetic neuropathy is a complex group of clinical syndromes that damage the different regions of the nervous system, either individually or in combination [1]. It is the most common and the most unpleasant complication of diabetes, leading to high morbidity and mortality, which results in large economic costs [2].

Assessment of the frequency of this damage in patients with diabetes is not simple and a wide range of various assessments are available depending on the applied criteria and methods for defining neuropathy. However, it can be said that diabetic neuropathy is the most common form of neuropathy, which is responsible for more hospitalizations than all other diabetic complications together. It should not be underestimated, because this "late" complication of diabetes can lead to foot ulcers and gangrene, lower leg and foot amputations, or even sudden death of a patient, presumably due to cardiovascular autonomic neuropathy [3].

The most common type of diabetic neuropathy, accounting for around 80% of all diabetic neuropathies, is a distal symmetric neuropathy, or otherwise called diabetic sensorimotor polyneuropathy [4], with initial symptoms in the feet, spreading upwards. Hyperglycemia is the most important modifiable risk factor for its emergence, as well as for other complications of diabetes, so a maximum control of glucose levels is the primary goal in diabetic patients [5].

The question then arises as to why additional remedies for neuropathy are continuously searched for, considering that a reliable control of blood glucose levels is possible. First, because despite considerable effort, the desired level of metabolic control is often not achieved [6], and second, despite the ideal glucoregulation, a significant number of patients with diabetes still experience neuropathic damage. A recent meta-analysis suggests that a constant glucose control prevents the development of clinical neuropathy only in type 1 diabetes, whereas in type 2 no reduction in incidence is found [7]. The quality of life of these patients is often very poor. This indicates a problem of early diagnosis and a successful treatment action, which should be individualized.

In the clinical practice, a large number of drugs and therapeutic procedures exist, which do not always lead to improvements. Drugs are divided into two groups: symptomatic treatment, or coanalgesics, and a therapy that presumably acts on the pathogenesis of diabetic polyneuropathy. Our observational study dealt with the monitoring of the neurophysiological state in diabetic polyneuropathy. Originally, we planned that the group of patients who received gabapentin for painful diabetic neuropathy serves as controls. However, due to insufficient understanding of the mode of action of this drug in neuropathic pain, we could not conclude with certainty about its possible impact on the status of the peripheral neurons or its potential impact on the pathogenesis. Therefore, the electrophysiological examination was carried out on patients without any therapy that could have had an impact on the state of the peripheral neurons. Gabapentin (GBP) belongs to the group of alfa 2-delta ligands, along with pregabalin, and they have been examined in several studies [8] and are approved for use by the Food and Drug Administration (FDA) and the European Medical Agency. There is data that pregabalin has a more predictable and consistent pharmacokinetic profile and could be titrated faster and easier to use in comparison to gabapentin [9].

Benfotiamine (BENTO) the thiamine monophosphate synthetic analogue, has improved bioavailability compared with thiamine [10]. It also has a preventive effect on microvascular complications in rats, without affecting the glycemic control [11]. Some short-term studies, lasting 8–12 weeks, have suggested its favorable impact on polyneuropathy [12], and along with its widespread use, we chose it for our research. However, probably the longest used and most thoroughly studied drug for diabetic neuropathy (Study 1 Sydney, Sydney 2, etc.), as confirmed by recent research, is alpha-lipoic acid (ALA) [13, 14], which has been shown to have a significant impact on the improvement of diabetic polyneuropathy.

The aim of this study was to study the effects of alpha-lipoic acid, benfotiamine and gabapentin on electrophysiological parameters of the state of peripheral nerves in diabetic polyneuropathy, with a control group of patients without any treatment. In addition, we aimed to determine the differences among the applied treatments and to estimate changes in individual electrophysiological parameters caused by the applied treatment.

Methods

The study was designed as an observational analytical study, with the purpose to determine whether the drugs used in the study have an effect in the treatment of peripheral nerve disorders in diabetic patients, which of them are more effective in the treatment of peripheral nerve injury, and to assess the needs for treatment in the controls in relation to the results of repeated electrophysiological findings.

Our study monitored the neurophysiological state in patients with diabetic polyneuropathy, who were referred to electromyoneurographic examination to the Electromyography Unit of the Neurology Clinic of the Clinical Center of Vojvodina by primary care physicians. Since the first control, the patients were subsequently recommended symptomatic treatment (gabapentin) or causally-related therapy (benfotiamine or alpha-lipoic acid), depending on the clinical picture, and electrophysiological examination at our unit was performed approximately for 3 months.

The choice of the drug was the exclusive responsibility of the neurologist performing an electrophysiological examination, and it is of note that for the last several years we have utilized the above-stated drugs. This was a standard procedure at our unit, however, patient's personal preferences were also taken into account and it could be determined only on the control examination whether the patient received the appropriate treatment. Originally, we had intended to recruit patients who received coanalgetic (gabapentin) as controls, but the control electrophysiological examination showed that a significant number of these patients did not take the recommended treatment, so these patients were taken

as controls. On the other hand, we had the opportunity to observe whether gabapentin still has some influence on the condition of the peripheral neurons.

The research was done as a prospective study. In the period over one year, we examined and analyzed a total of 120 patients with diabetic polyneuropathy, who were selected from patients examined at our Electromyography Unit. Each patient underwent electromyoneurographic examination, and data was collected according to a protocol in two acts: for the first time during the examination of patients before the introduction of the study drug, and the second time on the follow-up examination after three months. The inclusion criteria for the study were: patients with type 2 diabetes mellitus regularly referred by primary care physicians to electromyoneurographic examination aged 40–60 years. The exclusion criteria were: a history of other diseases and conditions that could lead to polyneuropathy and patients who during the study period stopped taking the study drug for some reason.

The criterion for dividing subjects into four groups was the drug they received, including a group who during the three-month period did not receive any medication: patients who received 600 mg of alpha-lipoic acid per day, patients receiving 600 mg of benfotiamine *per* day, patients receiving 900 mg of gabapentin *per* day, and patients who did not receive any medication Each group comprised 30 patients; Neurophysiological examination was performed at the Electromyography Unit in the following way: Electrophysiological indicators were studied by the two-channel MEDELEC system Synergy. We used methods of conventional electromyoneurography without the employment of insertion and denervation activity and innervation sample because it was not possible to exactly compare the quantitative data. Therefore we used stimulation methods of neurography with registering the EP on standard places while keeping the room temperature at around 25° C, and the patient's extremity skin temperature at around 32° C. The following parameters were recorded: motor conduction velocity (MCV) – ref. 48.3 ± 3.9 > 40 m/s, distal latency (DL) – ref. 5.1 ± 2.3 or ≤ 5.0 ms, sensory conduction velocity (SCV) – ref. 58.8 ± 5.8 (47m / s), F wave minimal latency (F min) – ref. for *nervus peroneus* 48.4 ± 4.0 (55 ms, modified for our laboratory), and the time span of F waves or F wave chronodispersion (ChrD) – for our laboratory the reference value of 2.4 ± 1.2 (5 ms). ChrD means the time difference between the minimum and maximum latency (10 consecutive stimulations).

In this study, we used the following statistical methods: for the measurement of central tendency we used descriptive analysis, which included the mean, while measures of variability included the standard deviation; for testing of the statistical hypothesis we used *t*-test; the multivariate analysis of variance (MANOVA) was used for comparisons of sample means of dependent variables.

Results

Patients in all study groups had moderately abnormal electrophysiological parameters, with signs of impairment of long fibers. Patients treated with alpha-lipoic acid or benfotiamine had mild pain, rated on Numeric Pain Rating Scale (NPRS) < 4. Patients treated with gabapentin had NPRS > 4, whereas controls had NPRS < 3. There were 55% of male and 45% female patients, aged 40–60 years, in average 46.5.

Table 1 shows that the initial motor conduction velocity before the applied therapy (MCV-i) and final motor conduction velocity after the three months of treatment (MCV-f) differed in all tested groups. Taking into account the reference values, we can observe that the application of the neuroprotective agents, alpha-lipoic acid and benfotiamine, increased, but not significantly, motor conduction velocity. In addition, the symptomatic treatment by coanalgesic gabapentin reduced motor conduction velocity. In the control group, where no treatment was applied, there was also a reduction in motor conduction velocity.

Table 2 shows that the application of neuroprotective therapy, alpha-lipoic and benfotiamine, caused shortening of distal latency, which is an indicator of improvement, but dif-

Table 1

The effect of the treatment on motor nerve conduction velocity in patients with diabetic polyneuropathy

Treatment	MCV-i (m/s)	MCV-f (m/s)	*t*	*p*
ALA	41.220	42.910	1.534	0.130
Benfo	40.610	41.113	0.670	0.505
GBP	40.980	40.493	0.712	0.479
Controls	40.080	39.690	0.545	0.588

MCV-i – initial motor conduction velocity; MCV-f – final motor conduction valocity; ALA – allpha-lipoic acid; Benfo – benfotiamine; GBP – gabapentin; controls – no treatment.

Table 2

The effect of the treatment on initial distal latency (DL-i) and final distal latency (DL-f) in patients with diabetic polyneuropathy

Treatment	DL-i (ms)	DL-f (ms)	*t*	*p*
ALA	5.350	5.133	0.769	0.445
Benfo	5.458	5.323	0.734	0.466
GBP	5.420	5.557	1.057	0.295
Controls	5.717	5.980	1.668	0.101

ALA – alpha-lipoic acid; Benfo – benfotiamine; GBP – gabapentin; controls – no treatment.

ferences were not statistically significant. On the other hand, the application of gabapentin and no treatment in controls led to prolongation of distal latency, i.e. deterioration of the condition, but also with no statistical significance.

Table 3 increased shows that the sensory conduction velocity after application of alpha-lipoic acid was significantly increased ($p < 0.05$). The application of gabapentin and no treatment in the control group showed a reduction in SCV. In the control group, this reduction was significant.

Table 4 shows that the application of the neuroprotective therapy with alpha-lipoic acid and benfotiamine caused shortening of F waves, whereas in the gabapentin group, as well as in the controls, there was a prolongation of F-waves, i.e. progression of the disease, but none of the differences reached statistical significance.

Table 5 shows that F wave chronodispersion was shorter after the application of the neuroprotective therapy; conversely, it was longer after the application of gabapentin or no treatment. However, these differences were not statistically significant.

lem are fewer. Great psychological and physical problems, as well as the economic costs of the disease, require a targeted, causal therapy. By development of electrophysiological diagnostics, diabetic polyneuropathy is much earlier diagnosed and quantified, although this method is still not widely available, so the clinical criteria are still prevalent. However, over the past few decades, this method has been used in research studies for assessment of severity and type of damage. On the other hand, the lack of an effective drug for the prevention and treatment has encouraged extensive research worldwide aimed at finding an efficient drug that would affect the pathogenesis of peripheral nerve injury [16].

In our observational-analytical study of 120 diabetic patients (type II diabetes) with distal symmetric polyneuropathy, there was a certain preponderance of males (55%), compared to females (45%). Although it is considered that at the age of 30–55 years androgens significantly favor atherogenic [17, 18], and thereby probably neuropathogenic effects in men, there are no significant differences in the clinical picture or therapeutic effects on the existing changes in

Table 3

The effect of treatment on initial sensory conduction velocity (SCV-i) and final sensory conduction velocity (SCV-f)

Treatment	SCV-i (m/s)	SCV-f (m/s)	*t*	*p*
ALA	31.353	35.350	2.292	0.026
Benfo	33.427	35.093	0.787	0.435
GBP	36.867	34.773	1.245	0.218
Controls	36.597	33.173	2.488	0.016

ALA – alpha-lipoic acid; Benfo – benfotiamine; GBP – gabapentin; controls – no treatment.

Table 4

The effect of initial treatment on F waves (Ftl-i) and final F waves (Ftl-f) in patients with diabetic polyneuropathy

Treatment	Ftl-i	Ftl-f	*t*	*p*
ALA	58.610	56.893	0.836	0.407
Benfo	59.697	59.530	0.117	0.907
GBP	59.450	61.197	1.393	0.169
Controls	59.967	62.160	1.682	0.098

ALA – alpha-lipoic acid; Benfo – benfotiamine; GBP – gabapentin; controls – no treatment.

Table 5

The effect of treatment on initial F wave chronodispersion (ChrD-i) and final F wave chronodispersion (ChrD-f)

Treatment	ChrD-i	ChrD-f	*t*	*p*
ALA	10.680	9.290	1.197	0.236
Benfo	12.300	10.757	1.504	0.138
GBP	9.733	13.433	1.533	0.135
Controls	9.353	10.920	1.889	0.064

ALA – alpha-lipoic acid; Benfo – benfotiamine; GBP – gabapentin; controles – no treatment.

Discussion

Diabetic neuropathy as a complication of diabetes leads to microvascular damage, including small blood vessels that supply the nerves of *vasa nervorum*. Therefore, diabetic neuropathy is a degenerative disease that leads to progressive disability, affecting peripheral nerves, namely pain fibers, motor neurons and autonomic fibers [15], and can affect all organs that are innervated. Most treatments are symptomatic, while therapeutic options that eliminate the root of the problem are fewer. Great psychological and physical problems, as well as the economic costs of the disease, require a targeted, causal therapy. By development of electrophysiological diagnostics, diabetic polyneuropathy is much earlier diagnosed and quantified, although this method is still not widely available, so the clinical criteria are still prevalent. However, over the past few decades, this method has been used in research studies for assessment of severity and type of damage. On the other hand, the lack of an effective drug for the prevention and treatment has encouraged extensive research worldwide aimed at finding an efficient drug that would affect the pathogenesis of peripheral nerve injury [16].

In our observational-analytical study of 120 diabetic patients (type II diabetes) with distal symmetric polyneuropathy, there was a certain preponderance of males (55%), compared to females (45%). Although it is considered that at the age of 30–55 years androgens significantly favor atherogenic [17, 18], and thereby probably neuropathogenic effects in men, there are no significant differences in the clinical picture or therapeutic effects on the existing changes in peripheral neurons in diabetic polyneuropathy. The average age of our patients was 46.5 years. The age differences were expected, because of the small age range we used in order to avoid the potential effect of age on the therapeutic response. The duration of DM was on average 8.2 years, ranging between 5 and 15 years. Our results convincingly show improvement of the condition of the peripheral nerves in subjects who received alpha-lipoic acid, which is in agreement with the results of other authors examining the influence of alpha-lipoic acid on larger samples and over longer time [19–21].

Although the statistical significance is not highly significant, it should be noted that this is a short-term study, and the very study design was such that it included subjects with advanced clinical diabetic polyneuropathy (referred by primary care physicians to specialists). Although alpha-lipoic acid showed a definite beneficial effect on all electrophysiological parameters, sensory conduction velocity was found the most sensitive, which may indicate that the effect is the strongest on the sensory nerve fibers. On the other hand, it can be concluded that this electrophysiological indicator is the most appropriate for the assessment of diabetic polyneuropathy. Efficacy of benfotiamine was also demonstrated in all electrophysiological parameters, but with less significance compared to alpha-lipoic acid. The favorable effects of benfotiamine, explained by an activating effect on transketolase and an inhibitory effect on alternative metabolic pathways in diabetic neuropathy, were confirmed in a recent study by the Hungarian author Várkonyi et al. [22], and even more convincing results were obtained by Norwegian researchers in their 24-month study [23], supporting our results. On the other hand, gabapentin had no impact on polyneuropathy and it is definite that this coanalgesic has no effect on the pathogenesis of diabetic neuropathy. In patients who received gabapentin, as well as in patients who did not receive any therapy, we found deteriorated electrophysiological parameters, or progression of polyneuropathy, although not with statistical significance, which is also explained by the relatively short duration of the study. Overall, sensory conduction velocity was proved to be the most sensitive neurophysiological indicator for detecting changes in the peripheral neurons, distal latency also showed a high sensitivity, while the sensitivity of other indicators was less significant. Therefore, it is recommended that the monitoring of diabetic polyneuropathy should involve primarily these two electrophysiological indicators.

Conclusion

Alpha-lipoic acid and benfotiamine had some impact on improving the neurophysiological parameters of peripheral neurons, in patients with diabetic polyneuropathy. Comparing the efficacy of these two drugs, we can conclude that alpha-lipoic acid was more effective. At the same time, we did not find electrophysiological signs of the benefits of the coanalgesic gabapentin on the condition of peripheral nerves or the course of polyneuropathy. Specifically, electrophysiological indicators were slightly worse in patients who received gabapentin, as well as in patients who did not receive any therapy, which indicates the progression of the damage of the peripheral neurons. In a relatively short period of three months there, we saw the deterioration of diabetic polyneuropathy in patients who did not receive therapy or received only symptomatic treatment and right improvement of polyneuropathy in groups of patients who received treatment for diabetic neuropathy. Therefore, an effective, 'neuroprotective' therapy should be applied continuously in this disease. The electrophysiological examination proved to be very precise and sensitive even in the case of small differences in the condition of the peripheral nerves, which indicates the need for regular electrophysiological monitoring of patients with diabetic polyneuropathy.

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Received on December 09, 2015.
Revised on January 11, 2016.
Accepted on January 14, 2016.
Online First September, 2016.