Brief Communication

Thioctacid is effective for neuropathy symptoms and hyperglycemia control without pronounced electromyographic changes

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Thioctic acid (TA) is a natural and strong antioxidant agent.[1] It is well-known that antioxidant therapy has good effects on nerve conduction in diabetic sensorial polyneuropathy (DSPN).[1] The DSPN is a frequently seen complication of diabetes. Metabolic causes result in axonal degeneration, and we know that short-term trials with the antioxidant TA appear to improve neuropathic symptoms in diabetic patients.[1] Treatment with TA 600 mg intravenous (iv) daily for 3 weeks represents a well-tolerated, and effective therapy for DSPN. Similarly, an oral dose of 600 mg daily administered for up to 5 weeks could offer benefits in symptoms and signs of DSPN without significant side effects.[2] Nerve conduction studies (NCS) are objective and reliable examinations in diabetics. The NCS give information regarding not only clinical changes, but also the effectiveness of the drugs.[2] In placebo-controlled trials studying the efficacy of parenteral, and oral alpha lipoic acid in the treatment of symptoms, clinical signs, and electrophysiology of diabetic sensor motor polyneuropathy, only one study revealed electrophysiological improvement.[3,4] In this study, we aimed to investigate the effectiveness of TA, and the relationship between therapy and nerve conduction studies in the treatment of symptomatic DSPN within a short period of one month.

In this before and after study, metabolically stable type 2 diabetic patients admitted to the Internal Medicine Department of Düzce Medical Faculty, Düzce, Turkey between April and July 2009 were evaluated. The DSPN has been accepted as present, if the patients have an abnormal NCS, and a symptom or symptoms (decreased sensation, positive neuropathic sensory symptoms predominantly in the toes, feet, or legs), or a sign or signs (symmetric decrease of distal sensation, or unequivocally decreased or absent ankle reflexes, or decreased vibration sense in great toe) of sensory motor polyneuropathy. Twenty volunteers who accepted the study protocol and completed visits were included in the study. Diabetic neuropathy symptom scores (DNSS), and attributes of NCS were recorded for every patient. The patients were randomly assigned to the treatment regimen: 1 x 600 mg TA/day (Gen Drug Company, Istanbul, Turkey) for one month, in addition to routine follow-up and therapy of other previous oral anti-diabetic agents. After one month, we assessed the DNSS and NCS once more. Then, the results of the patients (n=20) with DSPN, and completed one month follow-up period were statistically analyzed in this prospective study. After approval of the ethics committee of the Düzce University Medical Faculty, the present research was conducted in accordance with the Declaration of Helsinki. All subjects provided written informed consent before participation.

The DNSS was evaluated by a questionnaire, which was a 4-item symptom score scale for diabetic neuropathy.[5] The DNSS has the following items: (i) unsteadiness in walking; (ii) pain, burning, or aching of legs or feet; (iii) prickling sensations in legs or feet; and (iv) numbness in legs or feet. Every item has been scored as one point, and score indicating ≥1 were considered abnormal.

Electrophysiological attributes of bilateral sural, median, and ulnar sensory nerves, and left-sided tibial, peroneal, and median motor nerves were evaluated. All patients underwent conventional sensory and motor NCS. All studies were performed following standard techniques using an electromyography tool (Artoscan, Esaote Biomedica, Genoa, Italy) with surface recording and stimulating electrodes. The dorsal skin surface temperature of hands and feet was measured before each NCS. If the temperature was below 30°C, hot water, or an infrared heat source was used to raise it.

The distribution of nerve conduction values was tested by Kolmogorov-Smirnov Z due to the small number of groups, and was found normal in each group. Statistical analysis was performed to evaluate the changes between the first and second examination.

Statistical analyses were performed by mean and standard deviation, and Student's t-test for the parametric data and intergroup comparisons. Frequency distributions were analyzed by means of χ^2 tests. A $p \leq 0.05$ was considered significant. In addition, the relationship between DNSS, NCS results, and socio-demographic and clinical variables, that is age, gender, other diseases, diabetes duration, blood glucose levels, and glycosylated hemoglobin (HbA1c) levels were evaluated.

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Table 1 - Sociodemographic and clinical variables in patients included in a study at the Internal Medicine Department of Düzce Medical Faculty, Düzce, Turkey.

Variable	n	Mean ± standard deviation
Gender		
Male	9	
Female	11	
Age (year)	20	56.95 ± 7.56
Duration of diabetes (year)	20	8.75 ± 4.89
Duration of complaints (year)	20	2.97 ± 2.47
Glycosylated hemoglobin, mean (%)	20	
At first measurement		8.21 ± 2.04
At the second measurement		6.14 ± 1.47
Diabetic neuropathy symptom score	20	
At first measurement		1.75 ± 0.55
At the second measurement		0.85 ± 0.49
Fasting glucose level (mg/dL)	20	
At first measurement		191.45 ± 69.5
At the second measurement		148.85 ± 48.1

The socio-demographic and clinical variables of the patients are shown in **Table 1**. Previous histories of the patients have shown that 11 patients had hypertension, 9 patients had hyperlipidemia, and 4 patients had coronary artery disease. All patients were diagnosed with DSPN on clinical examination.

In the first examination, all patients complained of sensorial problems. We have found that 12 patients had hypoesthesia in the lower extremities, while 8 patients had hypoesthesia in 4 extremities on light touch. Vibration exam showed abnormalities in the lower extremities of 10 patients, but in all extremities of 6 patients. One patient reported absence of vibration in the lower extremities, and 3 patients had normal vibration sense. While 2 patients had a normal deep tendon reflex answer, 7 patients had decreased Achilles' reflexes. There was no answer in 11 patients. There was no difference between reflex examinations of the patients in the second examinations. The NCS results of 2 patients were normal. Fifteen patients had sensorial-motor axonal, and 3 patients had sensorial axonal polyneuropathy. Four of 15 patients with sensorial-motor axonal polyneuropathy had carpal tunnel syndrome also. Although the NCS results of the second evaluation were similar to the first one, most of the patients showed better results in the second evaluation. Shortened distal latencies, increased sensorial action potential and compound muscle action potential, and increased nerve conduction velocities were found in the second examinations.

The second DNSSs was lower than the first measurements in 90% of the patients (18 of 20 patients), and the same in the other 2 patients (p<0.001, **Table 1**). Similarly, there were significant differences in the comparison of fasting glucose and HbA1c levels also (**Table 1**). In correlation analysis between DNSSs and NCS results, age, gender, diabetes duration, duration of complaints, fasting blood glucose levels, and blood HbA1c levels, we have found that there were statistically significant, and positive correlations between DNSS and female gender, fasting blood glucose levels, and blood HbA1c levels (p<0.001). The relationship between DNSS and NCS was not significant. The DSPN is a commonly seen complication of diabetes, and there are more evidence of oxidative stress following hyperglycemia and free radical accumulation.[1] In our study, we studied latencies and amplitude action potentials. We found an absence of sural nerve answer in 13 patients. We stimulated the sural nerve in the second examination of one patient. Our findings support axonal degeneration and the role of polyneuropathy starting from the most distal part. The studies, in which the effect of TA evaluated on nerve conduction showed conflicting results. Only the study of Reljanovic et al[4] showed significant electrophysiological improvement of distal tibial motor, and sural sensory nerve latencies and velocities in their study, which was continued for 2 years. In our study, there was no statistically significant difference between the 2 NCS carried out with a one-month interval. Although we introduced standard dosage of TA, the short follow-up period may be a cause of this negative result. There was continued axonal degeneration in 11 patients, in whom sural nerve answer was absent as an evidence of axonal degeneration in diabetes.

Poor diabetes control (HbA1c>9%), age, and height were risk factors for DSPN.[6] We found a correlation between blood HbA1c levels and NCS. Blood glucose levels and HBA1c levels differed, but there was no significant difference between the 2 NCS. Many studies revealed that TA is effective for diabetes symptoms, but the TA's role and place in an algorithm among other commonly prescribed oral treatments for symptomatic relief of neuropathic pain in DSPN patients remains unclear.[2,7] Similarly, DNSSs improved after one month therapy by oral 600 mg TA, and the difference was statistically significant in our study (p<0.001). Blood glucose and HbA1c levels also improved. We used only TA, and did not make any drug regimen changes during this one-month period, so we believe that TA is not only effective for symptoms, but also effective for hyperglycemia control over a short period.

In conclusion, TA improved sensory symptoms and glycemia control within a one month period. Long-term trials that focus on neuropathy symptoms and conduction studies are needed to ascertain, whether oral treatment with TA over several years may slow, or reverse the nerve conduction problems of diabetic neuropathy.

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