Original Research Article

The efficacy of alpha-lipoic acid and/or gabapentin on the oxidant-antioxidant system in patients with diabetic polyneuropathy

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ABSTRACT

Background: Diabetic peripheral sensorimotor polyneuropathy is the most common complication seen in patients with diabetes mellitus (DM). Oxidant system plays a crucial role in its physiopathology. We investigated the changes in the serum levels of total antioxidant status (TAS), total oxidant status (TOS), paraoxonase-1 (PON1) and oxidative stress index (OSI) to evaluate the antioxidant efficacy of alpha lipoic acid (ALA) and/or gabapentin in patients with diabetic polyneuropathy (DPN).

Methods: Sixty-three type 2 DM patients with diabetic polyneuropathy (DPN) were enrolled in the study. Patients with DPN were divided into four groups in terms of their treatment: Group 1 consisted of treatment-naive patients; patients treated with ALA, gabapentin or combination of ALA and gabapentin comprised groups 2, 3, and 4, respectively. The patients received the medications for at least six weeks. Serum levels of TAS, TOS, PON1 and OSI were analyzed.

Results: No significant difference was observed between the groups according to the oxidative stress parameters studied.

Conclusions: The use of ALA and/or gabapentin in patients with DPN did not significantly affect the oxidative stress parameters, including TAS, TOS, PON1, and OSI.

Keywords: Alpha-lipoic acid, Diabetic polyneuropathy, Gabapentin, Paraoxonase-1, Total antioxidant status, Total oxidant status

INTRODUCTION

Diabetic polyneuropathy (DPN) is the most common complication in patients with diabetes. More than 50% of the patients with diabetes mellitus (DM), experience diabetic polyneuropathy.1

Among many mechanisms proposed for its pathophysiology, the most widely accepted one is the microvascular damage caused by the formation of reactive oxygen species (ROS) which leads to DPN.2

The aim of the treatment of DPN is to prevent neurologic damage and control the symptoms.3 Tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, antiepileptics, opioids and mexiletine have been proposed for the symptomatic treatment of DPN.4,5 Increase in ROS and oxidative stress plays an important role for the development of DPN.5-10 Thus, antioxidant drugs such as alpha-lipoic acid (ALA) can be used for the treatment of DPN.4 Neuroprotective and also pain-relieving effects of ALA therapy have been reported in the literature.1,2
Gabapentin, a gamma aminobutyric acid (GABA) analog, has an important role in the treatment of neuropathic pain, epilepsy and spasticity. In addition, the effects of gabapentin on the neuroprotection and oxidative stress have also been reported.

Oxidative stress has been defined as an imbalance between oxidant and antioxidant systems, occurring when the oxidant capacity exceeds the antioxidant capacity. Total antioxidant status (TAS), total oxidant status (TOS), paraoxonase-1 (PON1), the oxidative stress index (OSI) are parameters used for representing oxidative stress. TAS induced by hydroxyl radicals has antioxidative effect against the potent free radical reactions. TOS is related to the total amount of oxidant molecules. The ratio of TOS to TAS level is defined as OSI. PON1 reduces oxidative stress in lipoproteins, macrophages and the atherosclerotic lesions. Serum PON1 activities are effected by systemic lipid peroxidation stress and atherogenesis. Atherosclerosis is one of the significant factors causing DPN.

In previous studies conducted to define oxidative status in type 2 diabetes with or without polyneuropathy, increased TOS and OSI, while decreased TAS levels were reported regardless of the presence of concomitant neuropathy. However, levels of TAS, TOS, PON1 and OSI have not been studied in DPN patients receiving drug treatments. Besides the effectiveness of ALA and gabapentin in DPN is yet need to be clarified.

In this study, we investigated the effects of ALA and/or gabapentin on serum levels of TAS, TOS, PON1 and OSI to interpret their effects on oxidative stress in patients with diabetic polyneuropathy.

METHODS

Type 2 DM patients with a disease history of DPN more than 5 years based on clinical and electrophysiological findings were included in this study. The study was conducted in line with World Medical Association (WMA) Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects, and informed consent of the patients was obtained.

The study was approved by the local ethics committee. Patients receiving antioxidant drugs such as vitamin A, vitamin E, vitamin C, zinc, selenium, N-acetyl cysteine (NAC); neurotoxic medications such as chemotherapeutics; and also patients having endocrine and metabolic diseases that might cause peripheral polyneuropathy such as renal failure, folate deficiency, vitamin B12 deficiency, infections and peripheral vessel disease and also those with a history of cerebrovascular events, myocardial infarction, lumbosacral or cervical pathologies, cancer, and rheumatic disease were excluded from the study.

Patients meeting the inclusion and exclusion criteria mentioned above were randomly divided into 4 groups according to the treatment they received as follows: Group 1 was comprised of treatment-naive patients. Group 2, 3 and 4 were comprised of patients on treatment for at least 6 weeks receiving ALA 600 mg daily, gabapentin 900-3200 mg daily, combination of ALA and gabapentin, respectively.

For biochemical analyses venous blood samples collected in the morning after an overnight fasting were immediately centrifuged at 1500 g, and +4°C for 10 minutes.

The serums of the blood samples were pipetted into Eppendorf tubes and kept in the deep freezer at -80°C until the analysis. Measurements of the serum levels of TAS and TOS were performed using the automated measurement method developed by Erel. The reagents were supplied by Rel Assay Diagnostics, Mega Tip, Gaziantep, Turkey. OSI was calculated as the ratio of TOS to TAS according to following formula: (OSI= [TOS (µmolH2O2 Eq/L)/TAS (mmol Trolox Eq/L)] × 100).

Statistical analysis was performed using SPSS 15.0 (Chi., IL., USA) software. Descriptive statistics were expressed as the median (min-max), frequency and percentage. Intergroup evaluation was carried out using Kruskal-Wallis test. Values of p<0.05 were considered statistically significant.

RESULTS

A total of 63 patients (39 females) with the diagnosis of DPN were included in the study. Median age was 59 (range: 29-80) years and the distribution according to the groups are summarized in Table 1.

| Table 1: Patients characteristics in the four groups recruited according to the treatments. |
|-------------------------------------------|-----------|----------------|----------------|-----------|-----------|
| Patient numbers | Gabapentin | ALA | Gabapentin+ALA | Control | Total |
|-----------------|------------|-----|----------------|----------|--------|
| Age (year) median (min-max) | 56 (31-70) | 58 (29-74) | 60 (35-77) | 57 (27-80) | 56 (29-80) |
| Gender (male/female) | 8/11 | 4/10 | 4/2 | 8/16 | 24/39 |

ALA: Alpha lipoic acid
No statistically significant difference was found among the four treatment groups in terms of oxidative stress parameters including TAS, TOS, PON1 and OSI (p>0.05; Table 2).

**DISCUSSION**

We studied the effects of ALA and/or gabapentin on oxidative stress parameters including TAS, TOS, PON1 and OSI in patients with DPN. As a result we could not find any significant difference among these parameters in patients receiving ALA and/or gabapentin treatments.

The most widely accepted opinion in pathophysiology of DPN is the microvascular damage resulting from the formation of reactive oxygen species. Oxidative stress down-regulates Na-K-ATPase activity and leads to nerve ischemia. In hyperglycemia; increase in sorbitol, decrease in myo-inositol, activation of C-protein kinase and storage of immune-complex may lead to the development of DPN. In diabetics; inhibition of aldose reductase is achieved by the control of serum glucose; resulting in decrease in the production of sorbitol and ROS.

Antioxidants may be administered in the treatment of DPN since the oxidative system is effective in diabetic sensorimotor polyneuropathy.

Among these therapies, with its ameliorating effects on pain, ALA is the most promising drug as a prophylaxis in DPN, ALA is a fat and water-soluble sulfur-containing antioxidant.

Having anti-inflammatory, antioxidant, cytoprotective and neuroprotective properties, ALA contributes to the control of neuropathic pain with its effects on the underlying pathophysiologic mechanisms of diabetic sensorimotor polyneuropathy.

In the previous studies conducted to define oxidative status in type 2 diabetics with and without polyneuropathy, increased levels of TOS and OSI, but lower levels of TAS were found regardless of the presence of neuropathy. This study is the first one investigating the PON1 and OSI in patients receiving medications for DPN.

The effects of ALA on oxidative stress have been investigated in several different diseases in recent years. Since oxidative stress is an important risk factor for cardiovascular disease in haemodialysis patients, only increase in superoxide dismutase (SOD) levels was found to be statistically significant in the study investigating the effect of ALA on antioxidant enzymes such as SOD, catalase (CAT) and glutathione peroxidase (GPx).

Kolahi et al, investigated the effects of oral ALA on lipid peroxidation and antioxidant biomarkers in patients with rheumatoid arthritis (RA).

They reported that when the total antioxidant capacity (TAC), antioxidant enzymes SOD, GPx and arylesterase (ARE) activities and malondialdehyde (MDA)] were examined in patients given daily doses of 1200 mg ALA or placebo for eight weeks. A significant decrease in serum TAC was observed, but these changes in the ALA-treated group were not statistically significant compared to the group receiving the placebo. In addition, in the same study, statistically significant intra-, and intergroup differences in SOD and GPx levels were not detected.

As a result, ALA treatment did not affect the oxidative status in RA patients. The study of Kolahi et al supports our study and reports that ALA does not affect the oxidative status. However, they also emphasized the need to conduct larger scale studies. We also think that it is necessary to make evaluations with groups containing greater number of patients. Gabapentin is used in the treatment of neuropathic pain, epilepsy and spasticity. Although gabapentin is known to exert multiple effects, their mechanisms of action remain unclear. It increases GABA content in the neuronal tissue. Cerebroprotective effects of gabapentin may be associated with blockade of Ca++ channel and inhibition of nitric oxide. Rehling observed the neuroprotective effects of gabapentin in the hippocampus of rats. Coderne et al, emphasized the fact that excitatory amino acids are inhibited in the dorsal horn of the spinal cord with gabapentin. In their in vitro studies, Rothstein and Kuncl demonstrated that neural cell death was prevented by gabapentin therapy. Brito et al reported that gabapentin has anti-inflammatory effects and reduces the levels of inflammatory parameters.

There are a couple of limitations in our study such as the small number of patients, variable treatment periods, and different drug dosages.

| Gabapentin | ALA | Gabapentin+ALA | Control | P* |
|-----------|-----|---------------|---------|----|
| TAS**| 2.26 (1.65-3.89) | 2.03 (1.38-2.82) | 2.87 (1.46-2.30) | 2.96 (1.49-2.94) | 0.155 |
| TOS**| 8.39 (3.22-27.30) | 6.11 (3.27-12.13) | 6.30 (5.12-8.95) | 7.02 (2.64-30.31) | 0.704 |
| PON1***| 173.00 (43-262) | 107.50 (25-316) | 143.00 (132-166) | 135.50 (23-259) | 0.913 |
| OSI*| 0.38 (0.14-1.06) | 0.29 (0.16-0.62) | 0.38 (0.22-0.47) | 0.36 (0.13-1.53) | 0.824 |

*mmol/L Trolox Eq/L **µmol/L H2O2 Eq/L ***µL/L, **Kruskal-Wallis

ALA: Alpha lipoic acid, TAS: Total antioxidant status, TOS: Total oxidant status, PON1: Paraoxonase, OSI: Oxidative stress index
CONCLUSION

In our study, we investigated parameters such as TAS, TOS, PON1 and OSI that are important in evaluating oxidative stress in patients with DPN receiving ALA and/or gabapentin. It was shown that the use of ALA and/or gabapentin has no significant effect on these parameters. For evaluating more detail the efficacy of the treatments on DPN, there is a need for further comparative studies including the analyzes of several other molecules such as SOD, GPx, ARE and MDA indicating oxidative stress; with a larger number of patients.

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REFERENCES

1. Tang J, Wingerchuk DM, Crum BA, Rubin DI, Demaerschalk BM. Alpha-lipoic acid may improve symptomatic diabetic polyneuropathy. Neurologist. 2007;13:164-7.
2. Hosseini A, Abbodlaha M. Diabetic neuropathy and oxidative stress: therapeutic perspectives. Oxid Med Cell Longev. 2013;2013:168039.
3. Genuth S. Insights from the diabetes control and complications trial/epidemiology of diabetes interventions and complications study on the use of intensive glycemic treatment to reduce the risk of complications of type 1 diabetes. Endoc Prac. 2006;Suppl 1:34-41.
4. Savas M, Yeni E, Verit A, Gulum M, Aksoy N, Ciftci H, et al. Acute effect of phosphodiesterase type 5 inhibitor on serum oxidative status and prolyase activities in men with erectile dysfunction. Clinics (Sao Paulo). 2010;65:1311-4.
5. Kurizky L. Managing diabetic peripheral neuropathic pain in primary care. J Fam Pract. 2010;59(Suppl):S15-22.
6. McCluff CE, Rutkove SB. Critical appraisal of the use of alpha lipoic acid (thiotic acid) in the treatment of symptomatic diabetic polyneuropathy. Ther Clin Risk Manag. 2011;7:377-85.
7. Uzar E, Tamam Y, Evliyaoglu O, Tuzcu A, Beyaz C, Acar A, et al. Serum prolyase activity and oxidative status in patients with diabetic neuropathy. Neurul Sci. 2012;33:875-80.
8. Kamboj SS, Vasishtha RK, Sandhir R. N-acetylcysteine inhibits hyperglycemia-induced oxidative stress and apoptosis markers in diabetic neuropathy. J Neurochem. 2010;112:77-91.
9. dos Santos Sales IM, do Nascimento KG, Feitosa CM, Saldana GB, Feng D, de Freitas RM. Caffeic acid effects on oxidative stress in rat hippocampus after pilocarpine-induced seizures. Neurul Sci. 2011;32:375-80.
10. Vinket AM, Kato K, McLean LL, Soules ME, Feldman EL. Sensory neurons and schwann cells respond to oxidative stress by increasing antioxidant defense mechanisms. Antioxid Redox Signal. 2009;11:425-38.
11. Striano P, Striano S. Gabapentin: a Ca2+ channel alpha 2-delta ligand far beyond epilepsy therapy. Drugs Today (Barc). 2008;44:353-68.
12. Kale A, Börçek AO, Emmez H, Yildirim Z, Durdağ E, Lortlar N, et al. Neuroprotective effects of gabapentin on spinal cord ischemia-reperfusion injury in rabbits. J Neurosurg Spine. 2011;15:228-37.
13. Yokoyama H, Uchida H, Kuroiwa H, Kasahara J, Araki T. Role of glial cells in neurotoxin-induced animal models of Parkinson's disease. Neurol Sci. 2011;32:1-7.
14. Cakmak A, Soker M, Koc A, Erel O. Paraoxonase and aryleserase activity with oxidative status in children with thalassemia major. J Pediatr Hematol Oncol. 2009;31:583-7.
15. Aslan M, Sabuncu T, Kocyigit A, Celik H, Selek S. Relationship between total oxidant status and severity of diabetic nephropathy in type 2 diabetic patients. Nutr Metab Cardiovasc Dis. 2007;17:734-40.
16. Karsen H, Binici I, Sunnetcioglu M, Baran AI, Ceylan MR, Selek S, et al. Association of paraoxonase activity and atherosclerosis in patients with chronic hepatitis B Afr Health Sci. 2012;11:14-8.
17. Rosenblat M, Karry R, Aviram M. Paraoxonase 1 (PON1) is a more potent antioxidant and stimulant of macrophage cholesterol efflux, when present in HDL than in lipoprotein-deficient serum: relevance to diabetes. Atherosclerosis. 2006;187:74-81.
18. Demirdag K, Yilmaz S, Ozdarendeli A, Ozden M, Kalkan A, Kilic SS. Levels of plasma malondialdehyde and erythrocyte antioxidant enzyme activities in patients with chronic hepatitis B. Hepatogastroenterology. 2003;50:766-70.
19. Canales A, Sánchez-Muniz FJ. Paraoxonase, something more than an enzyme. Med J Clin. (Barc). 2003;121:537-48.
20. Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P, et al. Toronto Diabetic Neuropathy Expert Group. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care. 2010;33:2285-93.
21. Eckerson HW, Wyte MC, La Du BN. The human serum paraoxonase/aryleserase polymorphism. Am J Hum Genet. 1983;35:1126-38.
22. Vallianou N, Evangelopoulos A, Koutalas P. Alpha-lipoic Acid and diabetic neuropathy. Rev Diabet Stud. 2009;6:230-6.
23. Packer L, Kraemer K, Rimbach G. Molecular aspects of lipoic acid in the prevention of diabetes complications. Nutrition. 2001;17:888-95.
24. Rutkove SB. A 52-year-old woman with disabling peripheral neuropathy: review of diabetic polyneuropathy. JAMA. 2009;302:1451-8.
25. Oates PJ. Aldose reductase, still a compelling target for diabetic neuropathy. Curr Drug Targets. 2008;9:14-36.
26. Pop-Busui R, Sima A, Stevens M. Diabetic neuropathy and oxidative stress. Diabetes Metab Res Rev. 2006;22:257-73.
27. Mahdavi R, Khabbazi T, Safa J. Alpha lipoic acid supplementation improved antioxidant enzyme activities in hemodialysis patients. Int J Vitam Nutr Res. 2019;89(3-4):161-7.
28. Kolahi S, Mirtaheri E, Gargari BP, Khabbazi A, Hajalilou M, Asghari-Jafarabadi M, et al. Oral Administration of alpha-lipoic acid did not affect lipid peroxidation and antioxidant biomarkers in rheumatoid arthritis patients. Int J Vitam Nutr Res. 2019;89(1-2):13-21.
29. Oka M, Itoh Y, Wada M, Yamamoto A, Fujita T. A comparison of Ca2+ channel blocking mode between gabapentin and verapamil: implication for protection against hypoxic injury in rat cerebrocortical slices. Br J Pharmacol. 2003;139:435-43.
30. Rekling JC. Neuroprotective effects of anticonvulsants in rat hippocampal slice cultures exposed to oxygen/glucose deprivation. Neurosci Lett. 2003;335:167-70.
31. Coderre TJ, Kumar N, Lefebvre CD, Yu JS. Evidence that gabapentin reduces neuropathic pain by inhibiting the spinal release of glutamate. J Neurochem. 2005;94:1131-9.
32. Rothstein JD, Kuncl RW. Neuroprotective strategies in a model of chronic glutamate-mediated motor neuron toxicity. J Neurochem. 1995;65:643-51.
33. de Brito TV, Júnior GJD, da Cruz Júnior JS, Silva RO, da Silva Monteiro CE, Franco AX, et al. Gabapentin attenuates intestinal inflammation: Role of PPAR-gamma receptor. Eur J Pharmacol. 2020;873:172974.

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