Studying the Effect of Adding Alpha Lipoic Acid to Gabapentin to Improve Nerve Conduction Velocity and Glycemic Control of Patients with Diabetic Neuropathy
(Sample of Iraqi population)

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Abstract:

Diabetic neuropathy (DN) is the most common chronic complication of diabetes mellitus. Hyperglycemia-induced oxidative stress induces programmed cell death of nerves, which contributes to the pathology of Diabetic neuropathy. Many clinical trials depend on supplement, in an attempt to improve neuropathy symptoms such as (pain & tingling) and patient quality of life, one of them is alpha-lipoic acid (ALA). Alpha-lipoic acid is a potent anti-inflammatory and antioxidant with insulin-mimetic activity, it has been shown to improve clinical symptoms in experimental Diabetic neuropathy and protect peripheral nerves from ischemia, in addition to stimulate the nerve growth factor and promote fiber regeneration. This study is aimed to evaluate the effect of Alpha-lipoic acid supplement as adjuvant therapy to gabapentin in patients with diabetic neuropathy, which can reflect by the improvement in nerve conduction velocity (NCV) *a test was conducted to assess the severity of* iabetic neuropathy and clinical symptoms. A prospective randomized- open-label interventional study for 3 months include 33 DN patients, aged (18-69) years were divided into two groups; group A include 16 patients received gabapentin 300 mg once daily at night, and group B include 17 patients received gabapentin 300 mg once daily at night plus alpha-lipoic acid 600mg once daily. Pre and post 3 months of treatment, blood samples used to measure metabolic biomarkers (FBG, HbA1c), in addition to Nerve conduction velocity. The results showed that, the intervention group produced a highly significant change in HbA1c & no significant change in FBG levels after 3months of Alpha-lipoic acid supplementation. Meanwhile, there is no significant change in HbA1c & FBG levels in patients treated with gabapentin alone. Moreover, results showed highly significant improvement ($P<0.01$) in Nerve conduction velocity for two groups at the end of the study. Addition of Alpha-lipoic acid to gabapentin in diabetic neuropathy patients result to improve the glycemic control & Nerve conduction velocity.
after three months of treatment.

Key words: Diabetic neuropathy, Alpha lipoic acid, Gabapentin, Nerve conduction velocity.

دراسه تأثيراضافه حمض الفا ليبويك الى جابابنتين لتحسين سرعه التوصيل العصبي والسيطرة على مستوى السكر في الدم لمرضى اعتلال الأعصاب السكري

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الخلاصة:

اعتلال الأعصاب السكري هواكثر المضاعفات المزمنة شيوعًا لمرض السكري. يسبب الإجهاد التأكسدي الناجم عن ارتفاع السكر في الدم الى موت الخلايا المبرمجه للأعصاب ، مما يساهم في أمراض الاعتلال العصبي السكري. تعتمد العديد من التجارب السريرية على المكملات الغذائية في محاولة لتحسين أعراض الاعتلال العصبي مثل (ألالم,الوخز) ونوعية حياة المريض, أحدها هو حمض ألفا ليبويك . حمض ألفا ليبويك هو مضاد قوي للالتهاب ومضاد للأكسدة مع نشاط يحاكي الأنسولين، وقد ثبت أنه يحسن الأعراض السريرية في الاعتلال العصبي السكري التجريبي ويحمي الأعصاب الطرفيه من نقص الترويه ، بالإضافة إلى تحفيز عامل نمو الأعصاب وتعزيز تجديد الألياف. تهدف هذه الدراسة إلى تقييم تأثير إضافة حمض ألفا ليبويك كعلاج مساعد لجابابنتين في المرضى الذين يعانون من اعتلال الأعصاب السكري ، وهذا قد يعكسه التحسن في سرعة توصيل العصب والاعراض السريرية. استمرت الدراسة التداخلية العشوائية لمدة 3 أشهر وشملت 33 مريضًا يعانون من اعتلال الأعصاب السكري ، تتراوح أعمارهم بين (69-18) عامًا مقسمة إلى مجموعتين ؛ المجموعة (أ) تشمل 16 مريضا تلقوا الجابابنتين 300 ملغ مرة واحدة يوميا ليلا ، والمجموعة (ب) تشمل 17 مريضا تلقى جابابنتين 300 ملغ مرة واحدة يوميا ليلا بالإضافة إلى حمض ألفا ليبويك600ملغ مره واحده يوميا . قبل وبعد 3أشهر من العلاج ، استخدمت عينات دم لقياس مؤشرات التمثيل الغذائي(HbA1c,FBG)، بالإضافة إلى اختبارات سرعة التوصيل العصبي لتقييم شدة الاعتلال العصبي السكري. بعد 3 أشهر من استخدام حمض ألفا ليبويك ، أسفرت الدراسة عن تحسن كبير للغاية في مستويات HbA1c، ولكن ليس هناك تغيير كبير في مستويات FBG. وفي الوقت نفسه ، لا يوجد تغيير كبير في مستويات HbA1c و FBG في المرضى الذين عولجوا من جابابنتين وحده. علاوة على ذلك ، أظهرت النتائج تحسنا كبيرا (P<0.01) في سرعة التوصيل العصبي للمجموعتين في نهاية الدراسة. إضافة حمض ألفا ليبويك إلى جابابنتين في مرضى الاعتلال العصبي السكري ادى إلى تحسين السيطرة على نسبة السكر في الدم و NCV بعد ثلاثة أشهر من العلاج.

الكلمات المفتاحية: اعتلال الأعصاب السكري ، حمض ألفا ليبويك ، جابابنتين ، سرعة التوصيل العصبي.

Introduction

Diabetic neuropathy (DN) is one of the most common complications of diabetes mellitus, defined as peripheral nerve dysfunction [1]. It predisposes to severe functional limitations and serious complications including leg amputation [2]. There are three main alterations involved in the pathologic process of DN: first, Inflammation induces activation of nuclear factor kappa B, activator protein 1, and mitogen-activated protein kinases. Second, oxidative stress induced by hyperglycemia mediated by several pathways: polyol, hexosamine, protein kinase C, advanced glycosylation end-products, and glycolysis. Third, mitochondrial dysfunction accounts for most of the production of reactive oxygen species, these free radicals cause lipid peroxidation, protein modification, and nucleic acid damage, to finally induce axonal degeneration and segmental demyelination [3].

Treatment should be directed to reduce etiologic factors besides symptoms alleviation; several approaches have been evaluated to reduce neuropathic impairments and improve nerve conduction, such as oral anti diabetics, statins, antioxidants, anti-inflammatory, anticonvulsant, and other medications approved for neuropathy [4]. Alpha lipoic acid (ALA) is a coenzyme in the tricarboxylic acid cycle, its antioxidant properties can prevent and reduce micro and macro-vascular complications in diabetic patients, and that's why it considered as an effective therapy of DN. Experimental studies have shown that ALA will improve blood flow to the nerve, reduce oxidative stress and enhance distal nerve conductivity [5]. Supplementation with alpha lipoic acid improves levels of

blood glucose by preventing pancreatic islet cell harm [6]. ALA mimic insulin stimulating glucose uptake, the up regulation of adiponectin and the activation of adenosine monophosphate activated protein kinase (AMPK) in white adipose tissue, and has been shown to prevent hyperinsulinemia and insulin resistance [7]. In general, ALA efficiently reduces the level of glucose in type 2 diabetes patients by possibly enhancing a production of the insulin from a pancreas [8].

Patients and methods

A prospective randomized open-label interventional study designed to explore the effect of ALA supplement as adjuvant therapy in patients with DN in improving of the nerve conduction velocity (NCV). This study was conducted from October 2017 to 31th July 2018. The study was performed on 40 Iraqi patients of both genders (male & female) diagnosed with type 2 diabetic with neuropathy. All patients have been selected from the National Diabetes Center for Treatment and Research/ Mustansiriya University, following approval of the scientific committee in the National Diabetes Center. Seven patients excluded from the study due to incompliance and missed treatment dose (Only 33 patients completed the study). Patients were involved in the study were diagnosed with mild-moderate diabetic neuropathy, while severe cases of diabetic neuropathy and patients with other comorbid diseases or hypersensitive to any drug or supplement used in this study were excluded. The enrolled patients were followed up along the 3 months. They were categorized into two groups; **Group A**: included 16 patients treated with the conventional gabapentin capsules 300 mg as single daily dose at night. **Group B:** included 17 Patients treated with the conventional gabapentin capsules 300 mg as single daily dose at night plus ALA 600mg once daily for 3months. Patient's demographic details, presenting symptoms, history of diabetes, laboratory values relating to diabetes (FBS, and HbA1c) were recorded. *In addition to NCV* were conducted to assess the severity of DN **[9]**. All patients received their treatment for 3 months duration, and blood samples were collected at the beginning of the study (baseline values) and then after 3 months of starting treatment to measure the possible changes in the studied parameters.

Results

Demographic data and baseline characteristics of the patients included in the study are summarized in the table (1). In this table, there were non-significant variations among patients allocated in each group regarding to age, gender, body mass index (BMI), family history, duration of diabetes, duration of neuropathy symptoms, smoking & alcohol drinking.

Table (1): Demographic characteristics of patients with diabetic neuropathy

Demographic characters		Group A		Group B		P-value©
		N (%)		N	(%)	
Age (years)	≤ 60	7	(21.2)	7	(21.2)	0.881 NS
	> 60	9	(27.3)	10	(30.3)	
Gender	Male	8	(24.2)	8	(24.2)	0.866 NS
	Female	8	(24.2)	9	(27.4)	
BMI (kg/m2)	< 18.5	0	(0)	0	(0)	0.087 NS
	18.5 - 25	4	(8)	2	(4)	
	> 25	12	(24)	15	(30)	
Family History	Yes	14	(28)	11	(44)	0.246 NS
Duration of neuropathy symptoms	< 1 year	2	(6.1)	4	(12.1)	0.679 NS
	1-5 years	9	(27.3)	10	(30.3)	
	> 5 years	5	(15.2)	3	(9.1)	
Duration of Diabetes	< 10 years	1	(3)	4	(12.1)	0.166 NS
	≥ 10 years	15	(45.5)	13	(39.4)	
Smoking	Yes	3	(9.1)	2	(6.1)	0.576 NS
Alcohol	Yes	0	(0)	0	(0)	1.0 NS

Data presented as (N): Number of patients, (%) Percentage, ©Chi square test (χ^2) test for the goodness of the fit used to assess counts between groups. NS: No significant changes ($p \geq 0.05$)

Effect of the treatment on glycemic control is shown in table (2). There were no significant differences in the FBG & HbA_{1c} levels ($P \geq 0.05$) between both groups at the end of the study. However, patients received ALA in addition to gabapentin (group B) demonstrated a highly significant reduction in the HbA_{1c} levels, while no significant reductions were reported in group A for both FBG & HbA_{1c} levels.

Table (2): Effect of treatment on FBG & HbA_{1c} levels in patients with diabetic neuropathy.

Study Groups		Group A		Group B		P-Value [a]
FBG	Pre	225.94	90.98	196.12	64.17	0.283 NS
	Post	188.69	94.69	174.88	37.49	0.582 NS
P-Value [b]		0.084 NS		0.070 NS		
HbA1c	Pre	9.09 ±	1.31	9.28 ±	1.21	0.671 NS
	Post	8.73 ±	1.14	8.62 ±	0.79	0.683 NS
P-Value [b]		0.41 NS		0.001**		

Data shown as the mean ± SD, [a] One-way ANOVA used to test statistical differences between groups (vertically), [b] Paired t-test for comparison before & after within each group. NS: No significant changes ($p>0.05$), ** highly significant changes ($p<0.01$).

Influence of the treatment on NCV is shown in table (3) when the study is finished, highly significant improvement ($P<0.01$) is dominant for both groups in respect to the pre-treatment score of each group. However, the differences between groups at the end of the study are also highly significant

(P<0.01) for sensory sural and motor peroneal neuron, but in sensory & motor ulnar wrist, the results produced a significant alteration (P<0.05).

Table (3): Effect of treatment on the nerve conduction velocity in patients with diabetic neuropathy.

Study Groups		Group A			Group B			P-Value [a]
sensory sural (calf)	Pre	31.56	±	3.78	34.75	±	4.50	0.137 NS
	Post	32.67	±	1.50	39.25	±	5.35	0.002**
P-Value [b]		0.001**			0.001**			
motor peroneal (ankle)	Pre	34.44	±	3.17	35.58	±	4.21	0.506 NS
	Post	36.22	±	2.64	41.42	±	3.90	0.002 **
P-Value [b]		0.001**			0.001**			
sensory ulnar wrist	Pre	39.78	±	2.54	40.92	±	4.14	0.477 NS
	Post	41.56	±	2.60	45.42	±	4.68	0.039*
P-Value [b]		0.001**			0.001**			
motor ulnar wrist	Pre	44.33	±	5.45	43.42	±	4.60	0.681 NS
	Post	44.56	±	1.67	47.75	±	3.14	0.012 *
P-Value [b]		0.001**			0.001**			

Data presented as mean ± SD, [a] One-way ANOVA used to test statistical differences between groups (vertically), [b] Paired t-test for comparison before & after within each group. NS: No significant changes (p>0.05), (*) significant changes (p<0.05), ** highly significant changes (p<0.01).

Discussion

Considering demographic and disease characteristic of the studied patients, the mean age of the patients in this study was 60.26 years. Even though deals with a small sample of population, the mean of age is similar to that reported in other studies [10, 11]. This is attributed to the fact that incidence of neuropathy increased with advanced age [12]. The average duration of diabetes was 10.43 ± 3.42 years; prolonged exposure of peripheral nerves to hyperglycemia in long standing diabetics predisposes them to development of neuropathy. The role of glycemic control in development as well as progression of DN is supported by the available evidence [13].

Glycemic control (as assessed by FBS & HbA1C (%)) in this study was measured for all patients pre- and post-treatments. Only group B revealed highly significant decreased (p<0.01) in HbA1c levels at the end of the study. As an anticonvulsant medication, gabapentin is commonly used for treatment of neuropathic diabetes [14], there was no significant reduction in FBG levels in group B patients over the period of the current study, which comes in concordant with the study done by Majdinasab *et al*. (2019) that reported no significant effect of gabapentine on glycemic control [15].

Alpha lipoic acid administration can improve glucose homeostasis, raise glutathione concentrations, inhibit lipid peroxidation, and improve antioxidant enzyme activity, increase blood flow as well as uptake of glucose. It is decreases insulin resistance by activating adenosine monophosphate-activated protein kinase in skeletal muscle, endothelium and β-cells, as well as inhibition of hepatic gluconeogenesis [16,17]. Human studies revealed that ALA was assessed as a pharmacological means to increase glucose consumption & insulin sensitivity in patients with diabetes and peripheral neuropathy management [18, 19].

The most sensitive and specific technique for Diabetic neuropathy detection is the Nerve conduction velocity. The use of nerve conduction velocity for early diagnosis and follow-up in Diabetic neuropathy is recommended [20]. Table (3) shows the NCV for sensory and motor nerves at baseline and after 3 months in both groups. Comparison of the improvement in NCV at the completion of the study revealed highly significant improvement ($P<0.01$) in the two groups. Gabapentin may exert its effect by closing chloride channels in neural cells and opening calcium channels. Moreover, it can also alter the ion flow in the membrane channels, resulting in reduced post-synaptic inhibitory potential as well as augmented velocity flow in neural cells [21, 22]. Improvement in NCV by gabapentin has been reported in previous studies [22, 23]. However, another study reported no significant effect on NCV [24].

Alpha lipoic acid can directly eliminate the free radicals, inhibits peroxidation, improves blood flow, rises nerve Na^+-K^+ ATPase activity, defends endothelial functions in addition to improves nerve conductivity velocity [25, 26]. Furthermore, such data show that ALA benefits the vascular defects of DN and greatly enhances the function of the peripheral nerve. Additionally, ALA can improve the sensitivity to insulin [27]. Consequently, ALA is a good treatment option for DN. Since, the meta-analysis reported significant improvements in NCV [25].

Conclusion

Addition of ALA to gabapentin in patients with diabetic neuropathy resulted in improving NCV and the glycemic control of patients, in addition to decrease the severity and progression of neuropathy.

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