ORIGINAL ARTICLE

The Effect of Enalapril, an Angiotensin Converting Enzyme Inhibitor, on Diabetic Neuropathy: A Double Blind Random–Allocated Study

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ABSTRACT

OBJECTIVE: Diabetes mellitus is one of the most common endocrine diseases with micro-vascular complications and is a common cause of polyneuropathy. We studied the effect of enalapril on electrophysiologic criteria and clinical symptoms of patients with type II diabetes and sensory neuropathy.

MATERIALS AND METHODS: A double blind study was conducted on 45 Patients with type II diabetes and neuropathy. They were normotensive and randomly divided into case and control groups. The case group received oral enalapril 2.5 mg twice a day for 3 months. The control group received placebo. We evaluated the changes in symptoms and electrophysiologic findings.

RESULTS: In case group distal latency of peroneal ($p=0.01$), tibial ($p=0.2$), ulnar motor ($p<0.001$), ulnar sensory ($p<0.001$), median sensory ($p<0.001$), and median motor nerves ($p=0.004$) decreased.

Amplitude of peroneal ($p=0.01$), tibial ($p=0.01$), ulnar motor ($p<0.001$), ulnar sensory ($p<0.001$), median sensory ($p<0.001$) and median motor nerves ($p<0.001$) increased. Electrophysioloic test of peroneal n. ($p=0.01$), tibial n. ($p=0.01$), ulnar motor n. ($p<0.001$), ulnar sensory n. ($p<0.001$), median sensory n. ($p<0.001$) and median motor n. ($p<0.001$) increased. We did not get any result about sural sensory potential at the beginning and the end of the study. Neuropathy symptom score was also decreased. ($p=0.16$)

CONCLUSION: In case group electrophysiologic criteria of peroneal, tibial, median sensory and motor, and ulnar sensory and motor nerves showed significant improvement. But no significant changes were found in clinical symptoms.

KEY WORDS: Diabetic neuropathy, Enalapril, Electrophysiologic test.

INTRODUCTION

Diabetes mellitus (DM) is one of the most common endocrine diseases in the world.

It affects 5-8% of Iranian population (1). Diabetes is a common cause of polyneuropathy (2).

Some diabetic patients may suffer from a painful neuropathy leading to impairment of activities of daily living and mood disorder.

Recent studies have shown that ACE

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inhibitors delay progression of both diabetic neuropathy and postpone progression of disease (2). A double blind placebo controlled clinical trial with an ACE inhibitor (lisinopril) showed a 50% reduction in the progression of retinopathy over 2 years in patients with type I diabetes. (3).

We studied the effect of an ACE inhibitor (enalapril) on electrophysiologic criteria and clinical symptoms of the patients with type 2 diabetes mellitus and sensory neuropathy.

MATERIALS AND METHODS

A randomized double blind study was conducted on 50 patients aged 25-69 years with normotensive symptomatic type II diabetes. The patients were randomly divided into case and control groups (25 patients in each group). Patients were examined by a neurologist who was blind to the study. They were referred from the endocrine clinic. Physical exam, medical history and several ancillary work-ups such as lab tests were performed for all patients to rule out other causes of neuropathy. Patients who used such medications as carbamazepine that can affect the neuropathy were excluded from study. The neuropathy symptom score (NSS) (Appandix1) was assessed by a specific questionnaire including sensory symptoms (i.e. burning, numbness, tingling, aching, and cramp), their distribution and time of maximum intensity, and relieving and exacerbating factors. The patients were scored from 0 to 10 by this system. The neuropathy disability score (NDS-Appandix2) was obtained based on a clinical scoring system from a neurological examination that defined abnormalities of vibration perception, pin prick perception and temperature perception as well as the presence or absence of ankle reflexes, producing a score ranging from 0-10. Electromyography (EMG) and Nerve conduction study (NCS) was performed in four limbs by a neurologist (device: neurosacreen, Toennies, Germeny). Amplitude and distal latency were assessed in the proneal, tibial, sural, median (sensory and motor), and ulnar (sensory and motor) nerves at the beginning and the end of the study.

Patients with the fallowing findings were considered as suffering from neuropathy:

Proneal motor nerve conduction velocity less than 42 m/s and neuropathy disability score of less than 5.

Case group received 2.5mg enalapril oral twice a day for 3 months because in the higher dosage hypotension may occur. Control group received placebo. Changes in the neuropathy symptoms score and electrophysiologic findings were assessed in another center. Exclusion criteria consisted of a history of renal artery stenosis or a single kidney, vasodilator drugs consumption, history of thyroid or liver disease and history of hypertension (BP≥140 / 90). Color doppler sonography for both renal arteries was used to rule out renal function disorders.

Two patients from case group (one person died and another one didn't show off) and 3 patients from control group (they didn't show up again) couldn't continue to the end of the study. We used SPSS (ver 10) and paired t test for data analysis for NSS differences between case and control groups before and after treatment.

P value was demonstrated according to the statistics consultant with efficiency index of 95% and power of 80% in fifty people.

RESULTS

45 patients with diabetic neuropathy were assessed after 3 months.

2 patients form case group and 3 patients from control group excluded due to noncompliance. In case group, 3(13%) patients were males and 20(87%) were females. Other characteristics of the subjects are shown in Table (1).

There wasn't any significant difference in baseline characteristics between case and control groups.

Baseline nerve conduction study showed no significant difference between case and control groups. (Table 2)

In case group, peroneal nerve distal latency 0.14 ± 0.07 ms (p=0.01) decreased, but amplitude 0.39 ± 0.14 mv (p=0.01) and

Table 1- Base line characteristics

	Case	Control	**P value**
n	23	22	NS*
Age (years)	52.39±7.62	54.18±6.41	NS
Sex (M:F)	3:20	3:19	NS
Duration (years)	10.48±5.64	10.45±3.48	NS
BMI (Kg/m2)	27.30±2.07	26.50±1.93	NS
HbA_1C (%)	7.52±0.64	7.63±0.58	NS
FBS (mg/dl)	192.83±53.61	191.59±54.08	NS
Systolic BP(mmhg)	128.8±9.1	135±4.1	NS
Diastolic BP(mmhg)	77.2±10.1	79.2±8.3	NS

*None Significant

conduction velocity 1.09 ± 0.70 m/s (p=0.01) increased. In control group, peroneal nerve distal latency 0.10 ± 0.13 (p<0.001) increased, but amplitude 0.23 ± 0.14 mv (p<0.001) and conduction velocity 0.33 ± 0.16, m/s decreased (p<0.001).

Table 2- Comparison of baseline nerve conduction study in case and control group

	Case	Control	P value
Median motor	Baseline	Baseline	NS*
V(Conduction Velosity)	42.47±3.1	44.21±3.25	NS
DL(Distal Latency)	4.93±0.99	4.83±0.93	NS
A(Amplitude)	5.34±1.41	5.43±1.39	NS
Ulnar motor			NS
V	44.11±3.44	46.03±3.21	NS
DL	4.28±1.20	4.06±1.22	NS
A	5.38±1.55	5.42±1.62	NS
Peroneal			NS
V	35.09±3.38	36.34±3.08	NS
DL	5.29±0.64	5.21±0.63	NS
A	1.23±0.26	1.31±0.25	NS
Tibial			NS
V	33.37±3.12	33.96±3.19	NS
DL	5.25±0.84	5.28±0.86	NS
A	2.00±0.87	2.40±0.81	NS
Median Sensory			NS
V	40.38±3.65	42.29±2.76	NS
DL	3.53±0.53	2.65±0.35	NS
A	6.29±1.47	5.86±1.03	NS
Ulnar Sensory			NS
V	41.20±3.17	41.13±3.58	NS
DL	2.68±0.21	3.44±0.53	NS
A	5.78±1.03	6.32±1.46	NS
NSS	7.04±1.18	6.45±1.14	NS

*None Significant

Distal latency, amplitude and conduction velocity for median, tibial, ulnar motor and sensory nerves are shown in Table 3.

Sural nerve action potential at the beginning and the end of the study was not elicited. In case group mean NSS was 7.04 ± 1.18 and 6.96 ± 1.10 at the beginning and the end of the study, respectively (p=0.16) but in control group NSS was 6.45 ± 1.14 and 6.55 ± 1.14 at the beginning and the end of the study, respectively (p=0.16). (Table 3)

DISCUSSION

There is no medication available for relieving the symptoms of diabetic neuropathy. The best way in the treatment of these symptoms is optimal glucose control (4).

Cameron et al in 1992 showed that lisinopril can improve nerve blood flow and nerve conduction velocity in streptozotocin diabetic rats (5).

Two other studies in 1995 and 1996 showed an improvement in nerve conduction velocity after 12 weeks of treatment with lisinopril in patients with diabetic neuropathy and hypertension (6,7). The present study showed an improvement in electrophysiologic criteria (distal latency, amplitude, and conduction velocity) of the peroneal, tibial, median and ulnar (sensory and motor) nerves in patients with diabetic neuropathy. Neuropathy symptoms had no significant change. Lawrence et al in 2006 showed the same result as Cameron for streptozotocin diabetic rats (8).

The effect of ACE inhibitors is not only to reduce blood pressure, but also is to improve endoneurial blood flow, reduce the oxygen radical production with blocking NADPH oxidase and prevent peptide level decrease related to calcitonin, so they can prevent and improve diabetic neuropathy (8).

CONCLUSION

In case group, electrophysiologic findings (distal latency, amplitude and conduction velocity) of peroneal, tibial, median (sensory and motor), and ulnar (sensory and motor)

Table3- Comparison of Nerve conduction study in case and control group at end of study

	Case			Control		
Median Motor	Baseline	3 Months	P value	Baseline	3 Months	P value
V(Conduction Velocity)	42.47±3.1	44.45±2.92	<0.001	44.21±3.25	43.98±3.25	0.008
DL(Distal Latency)	4.93±0.99	4.74±0.92	0.004	4.83±0.93	4.91±0.95	0.004
A(Amplitude)	5.34±1.41	5.84±1.41	<0.001	5.43±1.39	5.25±1.37	0.008
Ulnar Motor						
V	44.11±3.44	46.33±3.13	<0.001	46.03±3.21	45.74±3.24	0.01
DL	4.28±1.20	4.08±1.17	<0.001	4.06±1.22	4.17±1.23	0.01
A	5.38±1.55	5.86±1.55	<0.001	5.42±1.62	5.22±1.63	0.01
Peroneal						
V	35.09±3.38	36.18±3.37	0.01	36.34±3.08	36.01±3.08	<0.001
DL	5.29±0.64	5.14±0.59	0.01	5.21±0.63	5.31±0.61	<0.001
A	1.23±0.26	1.62±0.26	0.01	1.31±0.25	1.08±0.19	<0.001
Tibial						
V	33.37±3.12	34.41±2.63	0.01	33.96±3.19	33.75±3.19	<0.001
DL	5.25±0.84	5.05±0.80	0.02	5.28±0.86	5.40±0.85	<0.001
A	2.00±0.87	2.50±0.79	0.01	2.40±0.81	2.19±0.80	<0.001
Median Sensory						
V	40.38±3.65	42.40±3.29	<0.001	42.29±2.76	42.05±2.78	0.001
DL	3.53±0.53	3.37±0.44	<0.001	2.65±0.35	2.80±0.38	0.001
A	6.29±1.47	6.74±1.40	<0.001	5.86±1.03	5.64±1.02	0.001
Ulnar Sensory						
V	41.20±3.17	43.30±2.65	<0.001	41.13±3.58	40.86±3.57	0.001
DL	2.68±0.21	2.52±0.18	0.002	3.44±0.53	3.56±0.54	0.004
A	5.78±1.03	6.27±1.01	<0.001	6.32±1.46	6.06±1.44	0.001
NSS	7.04±1.18	6.96±1.10	0.162	6.45±1.14	6.55±1.14	0.162

nerves significantly improved. Neuropathy symptom score showed no improvement. Additionally the control group had exacerbated electrophysiologic criteria but their NSS remained unchanged.

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Appendix 1- Neuropathy Symptoms Score (NSS)

Symptomatology: Foot/lower Leg	Yes	No	
Burning sensation	□2	□0	□Pt.
Numbness	□2	□0	
Paraesthesia	□2	□0	
Feeling of weakness(fatigue, exhaustion)	□1	□0	
Cramps	□1	□0	
Pain	□1	□0	□Pt.
Localisation			
Feet	□2		
Lower leg	□1		
Elsewhere	□0		□Pt.
Exacerbation			
Present at night	□2		
Present during day and night	□1		
Only present during the day	□0		
Patient is awakened from sleep By the symptoms	Score from		
	□1add		□Pt.
Symptom improvement when			
Walking	□2		
Standing	□1		
Sitting or lying down	□0		□Pt.
	Total score		□

Appendix 2- Neuropathy Deficit Score (NDS)

		side	right	left
Reflexes:	normal		0□	0□
	Diminished		1□	1□
	absent		2□	2□
Vibratory sensibility				
Measurement dorsal on big toe joint			right	left
	normal		0□	0□
	Diminished/ absent		1□	1□
Pain sensation				
Measurement on the dorsum of the foot			right	left
	normal		0□	0□
	Diminished/ absent		1□	1□
Temperature perception				
Measurement on the dorsum of the foot			Right	Left
	normal		0□	0□
	Diminished/ absent		1□	1□
		□Total score		