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ARTICLE

Alpha-lipoic Acid: Effects on the Beat-to-Beat Vectorcardiographic Parameters in Type 2 Diabetes Mellitus Patients with Cardiac Autonomic Neuropathy

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ABSTRACT

Objective: Relevance of cardiac autonomic neuropathy has not been fully recognized and there is no standardized treatment protocol. Aim: To evaluate the effects of alpha-lipoic acid on the beat-to-beat vectorcardiographic parameters, namely spatial QRS-T angle, QT dispersion (QTd) and corrected QT interval (QTc) in type 2 diabetes mellitus persons with cardiac autonomic neuropathy. **Research designs and methods:** Our study involved 33 persons with definite stage of cardiac autonomic neuropathy and diabetes mellitus type 2, which were assigned to each of two groups: one took standard antihyperglycaemic treatment (n=15, control group) and the other (n=18) in addition to standard therapy - 600 mg of alpha-lipoic acid daily for three months. The analysis of vectorcardiographic parameters was performed. **Results:** It was found out that alpha-lipoic acid contributed to decrease of the vectorcardiographic parameters, namely QRS-T angle, QTd and QTc. **Conclusions:** The positive influences of alpha-lipoic acid suggest the usefulness of its prescription to type 2 diabetes mellitus persons with definite stage of cardiac autonomic neuropathy. The efficacy of alpha-lipoic acid is the result of its direct effect on the parameters of vectorcardiography.

1. Introduction

Diabetes mellitus (DM) is a non-infectious illness with worldwide increasing prevalence. DM and state of chronic insulin resistance are associated with the development and progression of nervous and cardiovascular diseases. The pivotal role of chronic diabetic complications deve-lopment plays oxidative stress (OS), which is caused by an imbalance between accumulation and production of reactive oxygen species (ROS). Development of chronic hyperglycaemia is associated with endothelial nitric oxide synthase activity impairment and increasement of ROS production, thus resulting in diminished bioavailability of nitric oxide and increased OS [1-3].

Development of cardiac autonomic neuropathy (CAN) among patients with DM often causes heart rate control abnormalities and defects in vascular dynamics. Persons with decreased parasympathetic activity have a higher resting state heart rates due to development of vagal neuropathy that results in unopposed increased sympathetic outflow. Subjects with affection of both parasympathe-tic and sympathetic parts of autonomic nervous system

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have slower heart rates. By development of severe nerve dysfunction due to decrease in both parts of autonomic nervous system, heart rate is fixed [4]. Chronic hyperglycaemia can affect the autonomic nervous system and accelerate development and progression of autonomic dysfunction. Heart rate variability (HRV) is regulating by autonomic innervation, so cardiac autonomic dysfunction by DM is associated with a decrement of HRV [5,6].

Reversible prolongation of QTc (corrected QT for heart rate) in healthy persons can be caused by hyperinsulinaemia, and QTc prolongation can be caused by acute hypoglycaemia and chronic hyperglycaemia in diabetic as well as in healthy persons [7,8].

In DM patients prolonged QTc was found out during overnight hypoglycaemia, that was supported as an arrhythmic background for the development "dead in bed" syndrome [9].

Recent data from population-based trials could witness that the spatial QRS-T angle become an area of special scientific interest. The QRS-T angle is an electrocardiogram-derived measure of the difference in mean repolarization and depolarization vectors, can be defined as the angle between the mean QRS and T vectors. Widened QRS-T angle suggests about the abnormal arrangement of ventricular repolarization and has been defined as an independent and strong risk indicator for cardiac mortality and morbidity compared to electrocardiographic (ECG) risk indicators such as QT interval and other traditional cardiovascular risk factors [10,11]. The spatial QRS-T angle has been recently considered as an independent and strong predictor of sudden cardiac death and other morbid and mortal cardiac outcomes for various patient groups such as elderly subjects [13] and persons with chronic diseases, namely type 2 diabetes mellitus (T2DM) [10,11], heart failure and coronary artery disease (CAD)[12].

Given the role of OS in CAN progression, antioxidants demonstrated its effectiveness in prevention or delay of CAN diagnosis such as acetyl-L-carnitine, taurine and alpha-lipoic acid (ALA) the only water and fat soluble antioxidant [14-19].

Thus, we aimed to evaluate the effects of alpha-lipoic acid on the beat-to-beat vectorcardiographic parameters, namely spatial QRS-T angle, QT dispersion (QTd), QTc in persons with T2DM and definite stage of CAN.

2. Research Design and Methods

2.1 Patients

Our research was aimed to discover the effectiveness and safety of ALA on the vectorcardiographic parameters. 33 T2DM persons with definite stage of CAN were involved to the research. The median glycated hemoglobin A1c (HbA1c) of involved patients was 7.1%±0.4%, they were aged between 50-59 years and duration of diabetes mellitus was 1-6 years.

Patients were examined and treated by endocrinologist in the Department of Endocrinology of the Danylo Halytsky Lviv National Medical University, located on Lviv Regional State Clinical Treatment and Diagnostical Endocrinological Center.

The study was ethically approved by the Ethics Committee of the Danylo Halytsky Lviv National Medical University, protocol №2 from 18 February 2013 and was done according to the principles of the Helsinki Declaration (2004). All persons were orally informed about the study and provided a written consent prior to their enrollment in the research.

The clinical characteristics of the enrolled T2DM patients with definite stage of CAN are presented in Table 1.

Table 1. Clinical characteristics of patients involved to this research

Parameter	T2DM patients with definite stage of CAN (n=33)	
	Control (n=15)	Alpha-lipoic acid (n=18)
	Group 1	Group 2
Age (years)	55.33±0.95	54.83±0.87
Male gender (%)	53.3%/8	55.6%/10
Female gender (%)	46.7%/7	44.4%/8
Diabetes duration (yrs)	3.6±0.42	3.5±0.42
BMI (kg/m^2)	28.89±0.16	28.18±0.33
Medications		
ACE inhibitors (%)	80%/12	77.8%/14
β-blockers (%)	20%/3	11.11%/2
Metformin (%)	73.3%/11	55.6%/10
Sulfonylurea (%)	6.7%/1	5.5%/1
Combined hypoglycaemic therapy (%)	20%/3	38.9%/7
Hypertension (%)	80%/12	83.3%/15

Note:
ACE, angiotensin-converting enzyme; BMI, body mass index; CAN, cardiac autonomic neuropathy; T2DM, type 2 diabetes mellitus.

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2.2 Methods

The duration of the study was 2 years (2015–2017 yrs). Each patient included to the study was on the stable hypoglycaemic and antihypertensive treatment for 6 months and did not take ALA. The diagnosis of CAN was performed using the previously proposed diagnostical criteria [20]. After confirmation of definite CAN, patients were assigned to each of two groups: one took standard antihyperglycaemic treatment (n=15, control group) and the other (n=18) in addition to standard therapy - 600 mg of alpha-lipoic acid daily for three months.

Highly sensitive method of ion exchange liquid chromatography with D-10 analyzer and BIO-RAD reagents (United States) was used to measure HbA1c level and glucose oxidase method was used to determine the concentration of glucose in the blood.

All patients included in our study were assessed by measurement of resting 12-lead surface ECG with signal size of 10 mm/mV and a paper speed of 25 mm/s. QTc was calculated by dividing the QT interval by the square root of the preceding normal-to-normal (NN) interval time series (Bazett's formula: $QTc=QT/\sqrt{NN}$) [21]. The difference between the maximum and minimum QTc was defined as QTd. ECG-derived measure of the difference in mean vectors of depolarization and repolarization (QRS-T angle). The frontal planar QRS-T angle was calculated as the absolute difference between the frontal QRS wave axis and T-wave axis. If the difference exceeded 180°, then it was calculated by subtracting from 180° [22]. Resting ECG was carried out including the analysis of the following parameters: heart rhythm, heart rate, conduction intervals and Holter-ECG with the measurement of 24 hours ECG, HRV parameters and circadian indexes [(ECG "EC-3H" ("Labtech," Hungary)] analysis was performed [23].

2.3 Statistical Analysis

Statistical analysis was performed using the ANOVA (MicroCal Origin v. 8.0) software. Parametric t-test, non-parametric Wilcoxon t-test were used for comparisons between the two patient groups. Values are expressed as mean ± standard error of the mean (SEM). A p-value < 0.05 was considered as statistically significant.

3. Results

Comparing the HbA1c levels between both patient groups before and after treatment, we found out that HbA1c was not statistically significant changed after 3 months of the treatment period (P>0.05).

The features of the QTc, QTd and spatial QRS-T angle parameters in persons with T2DM and definite stage of CAN after treatment with ALA are shown in Table 2.

Table 2. Changes of the QTc, QTd and QRS-T parameters in T2DM persons with CAN after 3-months of alpha-lipoic acid therapy (Δ%, Mean ± SEM)

Parameter	T2DM persons with definite stage of CAN (n=33)			
	Groups	Baseline	After 3 months of treatment	% change from baseline
QTc (ms)	Control group (n=15)	433.4±6.45	427.8±4.72	-1.1±1.44%
	ALA (n=18)	418.3±8.1	396.3±5.51*	-4.9±1.39%
QTd (ms)	Control group (n=15)	50.3±4.53	46.0±4.98	-5.6±6.97%
	ALA (n=18)	58.2±4.75	45.1±3.19*	-18.1±5.2%
QRS-T angle (°)	Control group (n=15)	78.0±6.44	69.7±4.26	-6.1±5.52%
	ALA (n=18)	77.1±3.27	60.8±5.33*	-19.9±6.8%

Notes:
*The data are presented as absolute values and as % change from baseline, (Δ%, Mean ± SEM); *P<0.05, compared to baseline. CAN, cardiac autonomic neuropathy; QTc, corrected QT interval; QRS-T angle, spatial QRS-T angle; QTd, QT interval dispersion; T2DM, type 2 diabetes mellitus.*

Data, presented in Table 2 allows us to conclude that prescription of ALA to T2DM persons with T2DM and definite CAN is associated with statistically significant decrease in QTc [Δ=-4.9±1.39% (P<0.05)], QTd [Δ=-18.1±5.2% (P<0.05)] and the QRS-T angle [Δ=-19.9±6.8% (P<0.05)]. After 3 months of treatment period no statistically significant changes in the parameters QTc [Δ=-1.1±1.44% (P>0.05)], QTd [Δ=-5.6±6.97% (P>0.05)] and spatial angle QRS-T [Δ=-6.1±5.52% (P>0.05)] in the control group were found.

4. Discussion

The underlying mechanisms of QTc prolongation includes genetic factors, alterations in cardiac ion currents, cardiovascular autonomic imbalance, metabolic changes in myocardium, development of left ventricular (LV) hypertrophy, CAD [7]. The day-night modulation of the QT/relative risk relation-on 24-h ECG recordings was violated in persons with CAN and without CAD, in patients with LV hypertrophy or dysfunction, with an increased nocturnal QT rate dependence and reversed day-night pattern [24]. Reversible prolongation of QTc in healthy persons can be caused by hyperinsulinaemia, and QTc prolongation can be caused by acute hypoglycaemia or chronic hyperglycaemia in both diabetic and healthy persons [7, 8].

The changes in QTc can be considered as markers of

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cardiovascular autonomic dysfunction and as an important component in the potential prognostic value of the risk of arrhythmias [24]. Preserving the function of the parasympathetic nervous system in patients with T2DM with CAN performs a protective function, and the predominance of the sympathetic nervous system or the imbalance of LF/HF [low- (LF) and high-frequency (HF) bands in HRV] is harmful to the electrophysiological activity of the myocardium and may lead to changes in QRS-T [10,11].

Results of one recent trial showed that in persons with T2DM and CAN the value of spatial QRS-T angle is statistically significantly wider [11]. Furthermore, development and severity of CAN were independently associa-ted with the greater values of the spatial QRS-T angle. HRV parameters were significantly and independently associated with the spatial QRS-T angle, suggesting the presence of a pathophysiological ground linking the electrical, structural and functional myocardial disturbances in DM. Moreover, from the clinical viewpoint, presence of wider spatial QRS-T angle in T2DM patients may point out to the presence of CAN, which is often underdiagnosed [10].

In our previously investigations we have found out that T2DM persons with definite stage of CAN the QRS-T [78.3±1.95 (P<0.001)]; QTc [431.4±2.94 ms (P<0.001)] and QTd [53.7±1.49 ms (P<0.01)] were prolonged compared to persons without CAN [25]. An association between CAN and prolongation of QT interval was showed in many researches and it may predispose to sudden death in DM. Increased QTd was also proposed as a marker of diabetic cardiac neuropathy. Most of the data regarding QT interval and diabetic CAN are in T1DM with only few studies in T2DM [7,26].

Among patients with T2DM treated with ALA either i.v. or p.o. were observed improvements in glucose disposal. Results of other trials showed decrease in HbA1c, lipid peroxidation, antioxidant enzymes and inflammatory markers in patients receiving ALA. ALA has a function in decreasing damages caused by CAN and inflammatory factors as a compound with strong antioxidant potential [27-29].

A lot of unique effects of ALA, namely enhancement of glucose uptake, antioxidant effects, prevention of beta-cell destruction, inhibition of glycation reactions, improvement of neurons function and conduction, restoration of vitamins levels has been found in a several clinical and experimental study [1,2,6,11,14].

However, further randomized, controlled studies with inclusion of large patients' population and longer duration are needed to confirm the efficacy of ALA.

5. Conclusions

In conclusion, the positive influences of alpha-lipoic acid on decrease of the QRS-T angle, QTd and QTc are partly confirmed by its neurotropic, cardioprotective and angioprotective properties; suggests it efficacy in the complex therapy of persons with T2DM and definite stage of CAN.

Author Contributions

Victoria Serhiyenko - collection of material, statistical data analysis, writing the manuscript text; Krystina Kozlovska - management of the research, development of the study design, manuscript text editing; Alexandr Serhiyenko - management of the research, development of the study design, manuscript text editing. All authors contributed equally to the review. All authors have read and approve the final version of the manuscript.

Competing Interests

The authors have no conflicts of interest to declare.

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