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Effects of High-Dose α-Lipoic Acid on Heart Rate Variability of Type 2 Diabetes Mellitus Patients with Cardiac Autonomic Neuropathy in Korea (*Diabetes Metab J* 2017;41:275-83)

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Type 2 diabetes mellitus causes many kinds of chronic complications, such as microvascular complications including diabetic retinopathy, nephropathy, neuropathy, and macrovascular complications. Diabetic autonomic neuropathy (DAN) is also one of the most serious complications, and its prevalence varies depending on the cohort to 20% abnormality [1]. DAN may affect many organ systems, especially a wide spectrum of adverse cardiovascular outcomes [2]. Cardiac autonomic neuropathy (CAN) is associated with autonomic cardiomyopathy and is the pre-dispose factor of sudden cardiac death [3].

CAN is considered as a result of damages in the autonomic nerve fibers of heart that innervate the heart and blood vessels, which leads to abnormalities in heart rate control [4]. Therefore, diabetic cardiac autonomic dysfunction is inevitably associated with reduced heart rate variability (HRV) [5]. HRV has been proposed as an indicator of cardiovascular risk because the first manifestation of CAN is a decrement in HRV in a normal heart rate [6]. Glycemic control is considered as an essential treatment for CAN. According to Pop-Busui et al. [7], the early initiation of intensive glucose control in type 1 diabetes mellitus can help minimize the development of CAN. However, the benefit of glycemic control in type 2 diabetes mellitus is not confirmed [1]. Although blood sugar optimization is the most important treatment, it would be difficult to revive already advanced autonomic nervous system complications. Therefore, alternative treatments are needed based on the pathophysiologic aspect of diabetic CAN.

One of the possible solutions to treat diabetic CAN originate from that hyperglycemia can increase oxidative stress and cause direct neuronal damage and dysfunction [8]. Therefore, α-lipoic acid (ALA), which is known as a free-radical scavenger and used for treatment of diabetic peripheral polyneuropathy, could be regarded as one of treatment modalities for diabetic CAN by reducing the oxidative stress [9]. Fortunately, in the Deutsche Kardiale Autonome-Neurophathie (DEKAN) study, ALA showed a beneficial effect on HRV index of patients with diabetic CAN [10]. Another study, the Alpha Lipoic Acid in Diabetic Neuropathy (ALADIN) study, showed that ALA could improve neuropathic symptoms such as pain, burning, paresthesia, and numbness [11]. With such background, Lee et al. [12] investigated the effects of high-dose ALA on HRV of type 2 diabetes mellitus patients with CAN in Korea. In this study, the therapeutic effect of high-dose ALA to diabetic CAN presented a positive trend despite the lack of significant results. The standard deviation of normal-to-normal RR intervals, low frequency band and high frequency/low fre-

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quency ratio in the standing position increased in the ALA group after 24 weeks of trial. This result showed improvements in HRV indexes of ALA group. Moreover, the safety of high oral ALA therapy (1,200 mg/day) was verified from the similarity of the rates of overall abnormal reactions or severe adverse events between the ALA group and placebo group.

However, there are some questions in this study. The DEKAN study [10] and ALADIN study [11] showed significant improvements in HRV indexes and CAN. However, despite the high dosage (600 mg/day vs. 1,200 mg/day) and longer duration of treatment, the results of this study did not show significant improvements in HRV indexes. In addition to racial differences, further explanations and research are likely required to explain the different conclusions.

There was no assessment of diabetic control status in 75 subjects before the study period. Prior to the start of the study, if the information about glycemic control range or presence of microvascular complications was included, the therapeutic effect of ALA on patients with complications would be apparent. The baseline heart rate was 72.54±7.91 beats/min in ALA group and 70.60±7.35 beats/min in placebo group. Given that the heart rate was relatively stable at the time of registration, there is a possibility that the difference between the two groups was not statistically valid. Because HRVs appeared to be stable, severe neuropathy may not have progressed, so the effects of ALA in these patients could have been less. If the treatment effect is evaluated by dividing into the group of severe neuropathy and mild neuropathy, it is possible that the significance of ALA treatment is secured. In the present study, symptomatic improvements were not evaluated. Future evaluation of symptomatic improvements with a questionnaire will be interesting.

CAN is often overlooked despite serious cardiac complications such as sudden cardiac death. Therefore, it is necessary to develop a HRV marker with higher sensitivity such as 24 hours HRV monitoring tool. Another extensive and prospective study in large number cohorts will be needed to confirm the effects of the anti-oxidant on CAN and to seek alternative therapies.

This study showed a beneficial trend of ALA on CAN in type 2 diabetes mellitus patients. It is important to note that high-dose ALA with longer duration treatment is tolerable. Another extensive intervention study must be performed to confirm the effects on CAN.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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