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PHARMACOTHERAPY POSSIBILITIES OF CARDIOVASCULAR AUTONOMOUS NEUROPATHY IN CHILDREN WITH TYPE 1 DIABETES MELLITUS AT THE PRECLINICAL STAGE

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The aim of the article is to evaluate the effectiveness of the thioctic acid preparation in the complex therapy of type 1 diabetes mellitus (T1DM) in children with cardiovascular autonomic neuropathy at the preclinical stage.

Materials and methods. A design is a prospective randomized study. A clinical and instrumental examination of 64 children with preclinical stage signs of diabetic cardiovascular autonomic neuropathy (DCAN) was carried out. The cohort was divided into 2 groups: in the main and control groups, glycemic control was normalized by adjusting a dose of insulin therapy; in the main group, the children additionally received thioctic acid at the dose of 600 mg/day for 3 months. To control the effectiveness of the therapy, the technique of laser Doppler flowmetry was used.

Results. After the pharmacological intervention, there was an improvement in the disease course, normalization of carbohydrate and lipid metabolism, increased vasomotor mechanisms of the regulation of the tissue blood flow due to an increase in endothelial and neurogenic kinds of activity in combination with a decrease in the intravascular tone and an increase in the effective perfusion in tissues. An increase in the heart rate variability was detected, positive dynamics of cardiovascular tests indicators according to D. Ewing, temporal (pNN50%, SDNN) and spectral indicators (VLF) were diagnosed. Achievement and maintenance of the target values of glycemic control indicators, as well as the absence of glycemic variability, turned out to be clinically significant for reducing the manifestations of neuropathy. The non-invasive technique of laser Doppler flowmetry is informative for the early diagnosis of DCAN in T1DM children.

Conclusion. The carried out studies have demonstrated the effectiveness of the lipoic acid use at the dose of 600 mg/day for 3 months in the children with DCAN signs at the preclinical stage. The method of laser Doppler flowmetry for determining indications and monitoring the effectiveness of therapy makes it possible to implement a personalized approach to prescribing preventive treatment in T1DM children.

Keywords: diabetic cardiovascular autonomic neuropathy; α-lipoic acid; preventive treatment of complications in T1DM children; laser Doppler flowmetry

Abbreviations: GCP – good clinical practice; HbA1c – glicated hemoglobin; LADA – Latent Autoimmune Diabetes of Adults; MODY – maturity onset diabetes in youth; pNN50% – the mean number of times an hour in which the change in successive normal sinus (NN) intervals exceeds 50 ms; SDNN – standard deviation normal to normal; VLF – very low frequencies; AVA – arteriolo-venular anastomoses; ALA – Alphalipoic acid/α-lipoic acid; DCAN – diabetic cardiovascular autonomic neuropathy; VVR – vegetative-vascular regulation; ESPALIPON II – an octanoic acid bridged with *two* sulfurs; NATHAN I – Neurological Assessment of Thioctic Acid in Diabetic Neuropathy; LDF – Laser Doppler Flowmetry; HDLP- High-Density Lipoprotein; LDLP – Low-Density Lipoprotein; HR – heart rate; T1DM – type 1 diabetes mellitus; TG – triglycerids; ECG – electrocardiography; BMI – body mass index.

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RESEARCH ARTICLE

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ВОЗМОЖНОСТИ ФАРМАКОТЕРАПИИ НА ПРЕКЛИНИЧЕСКОЙ СТАДИИ КАРДИОВАСКУЛЯРНОЙ АВТОНОМНОЙ НЕЙРОПАТИИ У ДЕТЕЙ С САХАРНЫМ ДИАБЕТОМ 1 ТИПА

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Цель. Оценить эффективность препарата тиоктовой кислоты в комплексной терапии сахарного диабета 1 (СД 1) типа у детей с кардиоваскулярной автономной нейропатией на доклинической стадии.
Материалы и методы. Дизайн – проспективное рандомизированное исследование. Проведено клинико-инструментальное обследование 64 детей с признаками доклинической стадии диабетической кардиоваскулярной автономной нейропатии (ДКАН). Когорта ранжирована на 2 группы: в основной и контрольной группах проводилась нормализация гликемического контроля путём коррекции дозы инсулинотерапии; в основной группе дети дополнительно получали препарат тиоктовой кислоты в дозе 600 мг/сутки в течение 3-х месяцев. Для контроля эффективности терапии использовалась методика лазерной допплеровской флоуметрии.
Результаты. После фармакологической интервенции наблюдалось улучшение течения заболевания, нормализация показателей углеводного и липидного обмена, усиление вазомоторных механизмов регуляции тканевого кровотока за счёт увеличения эндотелиальной и нейрогенной активности в сочетании со снижением внутрисосудистого тонуса и увеличением эффективной перфузии в тканях, выявлено увеличение вариабельности ритма сердца, диагностирована положительная динамика показателей кардиоваскулярных тестов по D. Ewing, временных (pNN50%, SDNN) и спектральных показателей (VLF). Клинически значимым для уменьшения проявлений нейропатии оказалось достижение и поддержание целевых значений показателей гликемического контроля, а также отсутствие вариабельности гликемии. Неинвазивная методика лазерной допплеровской флоуметрии является информативной для ранней диагностики ДКАН у детей с СД типа 1.
Заключение. Проведенные исследования продемонстрировали эффективность применения липоевой кислоты в дозе 600 мг/сутки в течение 3-х месяцев у детей с признаками ДКАН на доклинической стадии. Метод лазерной допплеровской флоуметрии для определения показаний и контроля эффективности терапии позволяет реализовать персонализированный подход для назначения превентивного лечения у детей с сахарным диабетом 1 типа.
Ключевые слова: диабетическая кардиоваскулярная автономная нейропатия; α-липоевая кислота; превентивное лечение осложнений у детей с СД типа 1; лазерная допплеровская флоуметрия
Список сокращений: GCP – надлежащая клиническая практика; HbA1c – гликированный гемоглобин; LADA – латентный аутоиммунный диабет взрослых; MODY – диабет зрелого типа у молодых; pNN50% – процент (доля) последовательных интервалов, различие между которыми превышает 50 мс; SDNN – стандартное отклонение величин нормальных интервалов; VLF – очень низкочастотные; АВА – артериоло-венулярные анастомозы; АЛК – альфа-липоевая кислота; DECAN – Германское исследование кардиальной автономной нейропатии; ВСР – вегето-сосудистая регуляция; ДКАН – диабетическая кардиоваскулярная автономная нейропатия; ESPALIPON II – эффективность препаратов тиоктовой кислоты; NATHAN I – Неврологическая оценка эффекта тиоктовой кислоты при диабетической нейропатии; ЛДФ – лазерная допплеровская флоуметрия; ЛПВП – липопротеины высокой плотности; ЛПНП – липопротеины низкой плотности; ЧСС – частота сердечных сокращений; СД 1 – сахарный диабет типа 1; ТГ – триглицериды; ЭКГ – электрокардиография; ИМТ – индекс массы тела.

INTRODUCTION

Type 1 diabetes mellitus (T1DM) remains one of the most urgent problems of modern pediatrics due to the high level of disability and mortality [1, 2]. Alongside with the development of diabetology, an early detection and treatment of cardiovascular complications in children remain unresolved [2]. One of the most formidable complications of type 1 diabetes mellitus in children is diabetic cardiovascular autonomic neuropathy, which is characterized by denervation of the autonomic nervous system that regulates a vascular tone and a cardiac activity [1, 3]. Due to the complexity of diagnosing dia-

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betic cardiovascular autonomic neuropathy (DCAN), the data on the occurrence frequency are contradictory. The analysis of the literature shows that this index ranges from 20 to 60% [4, 5]. The main mechanism for the development of DCAN is microcirculatory disorders, which are accompanied by a decrease in the formation of nitric oxide, endoneural hypoxia, leading to the ischemic damage to nerve fibers [1, 6, 7]. Due to the development of glucose toxicity, metabolic disorders also play an important pathogenetic role [7–9]. There is a relationship between an increase in blood glucose levels and the severity of an oxidative stress. With hyperglycemia, there is an increase in lipid peroxidation, a violation of the nitric oxide formation by the vascular endothelium, an increase in the synthesis of pro-inflammatory adhesion molecules, and an increase in the sensitivity of smooth muscle cells of the vascular wall to vasoconstrictive stimuli [10–12]. The oxidative stress accompanies metabolic T1DM disorders in, which result in contributing to the development of late vascular complications.

Promising drugs for the treatment of DCAN are α-lipoic acid preparations, which have antioxidant, neurotrophic and hypoglycemic effects [8, 9, 13–15]. In diabetes mellitus in adult patients, the neuroprotective effect of alpha-lipoic acid (ALA) has been proven due to a decrease in the formation of advanced glycation endproducts of proteins in nerve cells, endoneural hypoxia and ischemia, as well as an increase in the concentration of the antioxidant glutathione [16–20]. In the DCAN study carried out by the German Cardiac Autonomic Neuropathy Research, the treatment of T1DM patients with DCAN by thioctic acid resulted in a significant improvement in the function of the nerve fibers of the autonomic nervous system, which was manifested by an increase in the heart rate variability [21]. The effectiveness of therapy in clinical DCAN is 30%, while the regression of disorders during the pharmacological intervention at the preclinical stage of DCAN is observed in 70% of patients [22, 23]. However, the studies on the pediatric population are singular, the indications and regimens for prescribing the thioctic acid preparation have not been determined, and the effectiveness of its use at the preclinical stage of DCAN has not been proven. One of the obstacles to the development of pathogenetic therapy for DCAN is the lack of “a gold standard” of preclinical diagnostics, which makes it possible to determine the indications for prescribing in this category of patients. It has been proven that the earliest changes in T1DM occur in the microvasculature. Therefore, an early functional diagnosis of cardiovascular complications, their dynamic control and the possibility of the early pathogenetic treatment are very important [1, 3, 10].

Currently, to assess the functional state of the microvasculature, a modern non-invasive technique of laser Doppler flowmetry (LDF) is used, which determines the tissue perfusion by measuring the Doppler frequency shift during probing and emitting a helium-neon laser at the wavelength of 632.8 nm and registering this radiation [9]. During the study, fluctuations in the blood flow in the microvasculature are recorded [24–27]. The use of LDF for the early diagnosis of DCAN opens up new prospects for personalized approaches to the preventive treatment of T1DM children.

THE AIM of the article is to evaluate the effectiveness of the thioctic acid preparation in the complex therapy of T1DM children with cardiovascular autonomic neuropathy at the preclinical stage.

MATERIALS AND METHODS

Study design

The principles of World Medical Association Declaration of Helsinki (WMA)[1] and the Rules of Good Clinical Practice (GCP)[2] of the Eurasian Economic Union served as the basis for a prospective, randomized, simple comparative study in parallel groups.

The Ethics Committee of the Federal State Budgetary Educational Institution of Volgograd State Medical University of the Ministry of Health of Russia (protocol No. 17 dated September 16, 2019) approved of the study. Written informed consent (IC) to participate in it was signed by all patients or their legal representatives prior to the inclusion in the research.

94 children aged 10 to 17 years with a verified diagnosis of T1DM, were examined. The exclusion criteria were: the age under 10 or over 17; T2DM, latent autoimmune diabetes in adults (LADA) and maturity onset diabetes in youth (MODY); the presence of primary arterial hypertension and other cardiovascular pathology not associated with T1DM; concurrent participation in another clinical trial; lack of a signed informed consent (IC) to participate in the study.

The withdrawal criteria were as follows: a refusal to participate in the study at any stage; decompensation of carbohydrate metabolism with ketoacidosis; somatic diseases at the acute stage in combination with T1DM.

Monitored parameters

The study was conducted on the basis of the endocrinology department of the Volgograd Regional Children’s Clinical Hospital. All patients underwent clinical, anamnestic and laboratory examinations, including the determination of fasting plasma glucose, HbA1c, total cholesterol, TG, LDLP, HDLP. The instrumental examination included the following: 24-hour ECG monitoring using the Cardiotekhnika-04-3 hardware-software complex (Inkart, Russia) under the conditions of free activity of

[1] Declaration of Helsinki by the World Medical Association (WMA). Ethical principles for conducting medical research involving a person as a subject. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013. Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

[2] Decision No. 79 “On Approval of the Rules of Good Clinical Practice of the Eurasian Economic Union” dated November 03, 2016. Available from: https://docs.cntd.ru/document/456026110

the subject, 24-hour blood pressure monitoring (ABRM-04 model, Meditech, Hungary); D. Ewing cardiovascular tests were performed: a slow breathing test (6 per minute), Valsalva test, Shelong test (orthostatic test), 30:15 test, an isometric load test. The assessment of the state of the microvasculature was carried out using the LDF method based on a two-channel laser Doppler flowmeter LAKK-OP (NPP LAZMA, Russia, Moscow) according to the attached methods for studying skin areas with arteriolo-venular anastomoses and without arteriolo-venular anastomoses. The basic state of microcirculation was assessed; the amplitude-frequency spectrum of perfusion fluctuations, the endothelial and neurogenic sympathetic activity, passive frequency ranges (respiratory and cardio rhythms) were analyzed [25].

After the examination, 64 children were diagnosed with DCAN signs of varying severity.

After the inclusion in the study, at the preclinical stage, the DCAN patients were divided into 2 groups by a simple randomization method. The main group included 32 children (15 girls and 17 boys), the mean age was 13.53±2.54 years; in the control group there were 32 children (16 girls and 16 boys), the average age was 13.15±2.03 years. The groups were comparable in terms of the age, sex, duration of the disease, the level of compensation for carbohydrate and lipid metabolism (Table 1). All the patients were on bolus insulin therapy, and the insulin therapy was adjusted if necessary. According to the ESPALIPON II study (the effectiveness of thioctic acid preparations), the same efficacy and safety of oral and infusion forms of thioctic acid at the dosage of 600 mg were proved. Therefore, the patients of the main group received a thioctic acid preparation (Lipoic acid, Marbiopharm, Russia) at the dose of 600 mg/day within 3 months. After 3 months, a re-examination was carried out.

Statistical processing

The Shapiro-Wilk test was used to assess the distribution of quantitative indicators. In the form of mean values (M ± SD), the results of the normal distribution of features are presented, in the non-normal distribution, the median (Me) and quartiles (25^{th} and 75^{th} percentiles) are presented. The non-parametric Wilcoxon test was used to assess the statistically significant difference in related quantitative traits. Contingency tables with the two-tailed Fisher's exact test were used to assess the significance of the relationship between two variables. At $p<0.05$, the difference was statistically significant. The statistical package STATISTICA 10.0 (StatSoft, Tulsa, USA) was used to process the results.

RESULTS AND DISCUSSION

For 3 months, the dose of insulin was adjusted to the patients under control by a pediatric endocrinologist. The indicators of carbohydrate metabolism are presented in Table. 2. During the observation period, the indicators of carbohydrate metabolism compensation improved in both groups. After 3 months, a decrease in the level of glycated hemoglobin was observed in most patients. However, in the group of the children treated with lipoic acid, there was a more significant decrease in the studied indicator than in the control group (7.45 [6.4; 8.2] and 7.9 [6.84; 9.1], respectively (p=0.0378). The presence of positive dynamics in the two study groups at once can be primarily explained by an increase in the level of patients' compliance during the participation in the study.

A more pronounced decrease in the level of glycated hemoglobin in the main group may be associated with the hypoglycemic effect of alphalipoic acid (ALA) due to improving the utilization of glucose by peripheral tissues and increasing insulin sensitivity (a decrease in the glucose-insulin index).

The improved glucose utilization by ALC tissues seems to be associated with phosphorylation of tyrosine residues of insulin receptors, activation of glucose transporters, and a number of other effects in insulin-dependent tissues. These factors increase glucose uptake by adipocytes and increase the activity of tyrosine kinase and serine/threonine kinase [28].

In 1999, in a placebo-controlled study, there was an increase in the insulin sensitivity in T2DM patients after a month of using ALA at the dose of 600 mg/day [29]. Ansar H. et al. [17] recorded a decrease in plasma glucose levels on an empty stomach and 2 hours after a meal, insulin resistance in T2DM patients while taking ALA at the dose of 300 mg/day. In another randomized study, in T2DM patients, taking ALA at the dose of 300 to 1200 mg/day for six months improved the glycemic profile and reduced indicators of an oxidative stress [30]. The multicenter, double-blind, placebo-controlled study NATHAN I (Neurological Assessment of Thioctic Acid in Diabetic Neuropathy) showed a decrease in HbA1c levels [31].

The systematic review and meta-analysis [13] of 20 randomized clinical trials investigating the effect of ALA on glycemic profile in the patients with metabolic disorders showed that its administration at the dose of 200–1800 mg/day from 2 weeks to 1 year, led to a decrease in glucose levels and fasting plasma insulin, HbA1c concentration and insulin resistance.

It is known that lipid profile indicators in T1DM children and adolescents depend on glycemic control [3, 8, 9]. In addition, dyslipidemia and hyperglycemia are the main pathogenetic factors of diabetic neuropathy, which lead to neurodegeneration through metabolic and inflammatory mechanisms. In T1DM children with lipid metabolism disorders, changes that indicate the initial manifestations of autonomic heart rhythm dysregulation in the form of hypersympathicotonia and electrical myocardial instability, have been identified [27].

In this study, all the groups were initially comparable in terms of lipid metabolism (Table 3). Lipid metabolism

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Table 1 – Clinical and laboratory characteristics of the groups under study

Indicator	Main group (n = 32)	Control group (n = 32)	p
Disease duration	5.12±3.1	4.96±4.35	p=0.87
Debut	7.86±3.12	8.2±4.28	p=0.72
Glucose variability	7.93±3.41	7.61±4.07	p=0.73
HbA1c level	8.2 [7.5; 9.6]	8.6 [7.3; 9.8]	p=0.85
Average daily insulin dose	0.97 [0.7; 1.01]	0.91 [0.67; 1.14]	p=0.82
Total cholesterol	4.34±0.86	4.22±0.94	p=0.60
Triglycerides	0.82 [0.48; 1.26]	0.79 [0.59; 1.21]	p=0.71
BMI	19.89±2.68	19.26±2.96	p=0.83

Table 2 – Indicators of carbohydrate metabolism in the study groups at baseline and after 3 months of therapy with thioctic acid

Indicator	Main group (n = 32)		Control group (n = 32)	
	Baseline	After 3 months of therapy	Baseline	After 3 months of therapy
Glucose variability	7.93±3.41	6.34±3.15	7.61±4.07	6.45±2.19
HbA1c level	8.2 [7.5; 9.6]	7.45*[1] [6.4; 8.2]	8.4 [7.3; 9.8]	7.9*[2]*[3] [6.84; 9.1]
Average daily insulin dose	0.97 [0.7; 1.01]	0.99 [0.81; 1.18]	0.91 [0.67; 1.14]	0.96 [0.75; 1.26]

Note: *[1]p=0.013 compared to baseline; *[2]p=0.019 compared to baseline; *[3]p=0.033 compared to group 1.

Table 3 – Indicators of lipid metabolism in the study groups at baseline and after 3 months of therapy with thioctic acid

Indicator	Main group (n = 32)		Control group (n = 32)	
	Initially	After 3 months of therapy	Initially	After 3 months of therapy
Total cholesterol	4.34 [3.91; 5.22]	4.07*[1] [3.69; 4.51]	4.28 [3.79; 5.31]	4.22*[2]*[3] [3.72; 4.98]
Triglycerides	0.82 [0.48; 1.26]	0.78 [0.46; 1.08]	0.79 [0.59; 1.21]	0.80 [0.58; 1.24]
LDLP	2.83 [2.33; 3.04]	2.25*[4] [2.07; 2.88]	2.96 [2.30; 3.11]	2.90 [2.28; 3.12]
HDLP	1.75 [1.26; 2.06]	1.89*[5] [1.34; 2.27]	1.78 [1.22; 2.14]	1.81 [1.20; 2.17]
Atherogenic index	1.89 ± 0.82	1.78± 0.71	1.87 ± 0.78	1.89±0.97

Note: *[1]p=0.028 compared to baseline; *[2]p=0.039 compared to baseline; *[3]p=0.031 compared to group 1; *[4]p=0.015 compared to baseline; *[5]p=0.044 compared to baseline.

disorders in 14 children in the study group (43.7%) and in 12 children in the control group (15.6%) were manifested as an increase in total cholesterol above the target values (>4.5 mmol/l). In 10 of them in the first group and in 9 in the second, an increase in LDLP was determined (>2.5 mmol/l). At the same time, the atherogenic index was within the normal range. In most children in the study group, the level of TG was within the reference values, however, in 5 children of the intervention group (15.6%) and in 7 children of the control group (21.8%) it was increased.

By the end of the study, the lipid levels had reached significant differences between the groups. The analysis of lipid spectrum indicators in the main and control groups revealed a statistically significant decrease in the level of total cholesterol (p=0.028 and p=0.039, respectively). It should be notified that by the end of the observation, a decrease in total cholesterol had been notified only in the children of the control group with a significant decrease in the level of glycated hemoglobin and glycemia (21.8%; 7/32). However, in the children of the intervention group who had been receiving lipoic acid, this indicator was significantly lower at the end of the study (p = 0.033).

The TG level had a pronounced downward trend in almost all patients in the main group (25/32), but it was not statistically significant (p = 0.22), and did not change in the control group, while there was no significant difference between the groups (p =0.29). However, it turned out that the children who had been receiving lipoic acid were significantly more likely to have a decrease in this indicator relative to outcomes (71.8% vs 28.1%, p = 0.024). The presence of positive changes in blood lipids in the comparison group can be explained by the improved control of hyperglycemia, as well as increased adherence of patients to medical prescrip-

Table 4 – Indicators of basic microcirculation and the amplitude-frequency spectrum of blood flow fluctuations in T1DM children in the area without arteriolo-venular anastomoses before therapy

Indicator	Main group (n = 32)	Control group (n = 32)	
	Initially	Initially	p
M	6.64 [4.37; 8.71]	6.28 [4.28; 7.57]	p=0.324
σ	0.845 [0.7; 0.96]	0.86 [0.7; 0.97]	p=0.76
Cv	12.89 [9.81; 16.34]	14.29 [10.01; 19.39]	p=0.042
P_{eff}	1.43 [1.14; 2.91]	1.51 [1.33; 2.06]	p=0.31
Ae	0.16 [0.12; 0.21]	0.19 [0.16; 0.27]	p=0.68
ET	4.67 [3.38; 6.08]	4.28 [3.21; 5.89]	p=0.46
Ae/3σ	7.16 [5.52; 9.95]	7.27 [5.32; 10.05]	p=0.37
Ae/M	2.61 [1.6; 4.18]	3.41 [1.4; 5.11]	p=0.56
An	0.21 [0.16; 0.3]	0.26 [0.21; 0.4]	p=0.34
NT	3.87 [2.87; 5.29]	3.89 [2.6; 5.84]	p=0.047
An/3σ	8.62 [6.81; 11.67]	8.44 [6.74; 10.61]	p=0.63
An/M	3.62 [1.84; 6.88]	3.04 [1.68; 7.34]	p=0.52
Am	0.23 [0.17; 0.34]	0.32 [0.21; 0.38]	p=0.08
MT	3.43 [2.22; 5.09]	3.2 [2.69; 4.58]	p=0.54
Am/3σ	7.84 [5.97; 13.63]	8.01 [6.03; 14.28]	p=0.28
Am/M	2.66 [1.95; 6.5]	3.02 [2.09; 7.86]	p=0.65
Ar	0.22 [0.17; 0.38]	0.28 [0,14; 0,42]	p=0.39
Ar/3σ	6.72 [5.16; 10.43]	6.84 [6.02; 9.89]	p=0.27
Ar/M	4.89 [3.14; 6.07]	4.62 [3.23; 5.54]	p=0.57
Ac	0.26 [0.24; 0.51]	0.24 [0.21; 0.49]	p=0.84
Ac/3σ	14.02 [11.03; 18.29]	12.82 [12.43; 17.49]	p=0.047
Ac/M	5.62 [3.25; 8.94]	5.17 [3.07; 7.36]	p=0.778
Ac/Ar	1.7 [1.22; 2.35]	1.57 [1.17; 2.67]	p=0.28
SI	0.94 [0.88; 1.09]	0.93 [0.75; 1.12]	p=0.08
IVT	0.66 [0.59; 0.85]	0.57 [0.56; 0.64]	p=0.37

Note: M – mean perfusion; σ – standard amplitude deviation of blood flow fluctuations; Cv – coefficient of variation; P_{eff} – effective perfusion; Ae – fluctuations of neurogenic nature; ET – endothelial tone; An – neurogenic fluctuations; NT – neurogenic tone; Am – fluctuations of myogenic nature; MT – myogenic tone; Ar – fluctuations of respiratory nature; Ac – fluctuations of cardiac nature; A/M – amplitude of fluctuations relative to mean perfusion; A/3σ – amplitude of fluctuations relative to mean modulation of blood flow; SI – shunt index; IVT – intravascular tone.

tions, strict adherence to dietary recommendations and lifestyle modifications during their participation in the study.

It has been established that ALA increases the synthesis of coenzyme A, promotes the transfer of fatty acids and acetate into the mitochondrial matrix, and also has a positive lipotropic effect [3, 9, 28]. Recent studies have shown that ALA shifts the spectrum of blood lipids towards unsaturated fatty acids, reduces the content of total cholesterol, and increases the HDLP fraction.

In the process of observation, in the main group of the children treated with lipoic acid, there was a statistically significant increase in HDLP (p=0.044). There were no significant changes in the control group, while the indicator, in general, tended to increase (p=0.19). The positive dynamics in LDLP was observed in the main group. By the end of the study, the level of this indicator had decreased (p=0.015), in the control group it had not changed significantly in most patients, while, in general, it had also tended to decrease in the group (p=0.24). These studies are consistent with the results obtained by other authors for T1DM and T2DM patients and indicate the ability of ALA to have a direct effect on lipid metabolism. So, Wollin S. et al. reported an increase in HDLP levels with the use of ALA [32] . In 2009, Gianturco V. et al. established that taking ALA at the dose of 400 mg/day reduces the indicators of an oxidative stress and the antiatherogenic fraction of cholesterol in T2DM patients [16]. In another study, Zhang Y. et al. also found out a decrease in cholesterol, LDLP and TG (p <0.01) with the use of ALA [33].

Cardiovascular autonomic neuropathy is detected at the early stages of the disease in DM patients and can be subclinical, i.e., it is manifested only in special tests [1, 4, 5, 22, 32]. The study of cardiovascular reflexes, which have a high sensitivity and a good reproducibility, is “a gold standard” for the clinical DCAN detection [1, 3, 5, 9]. Resting tachycardia is often an early clinical sign of developing neuropathy. In DCAN, the vagus nerve is the first to be affected, which leads to an increase in sympathetic influences on the heart and the appearance of resting tachycardia. In this study, resting tachycardia was initially detected in 11 children in the main group (34.4%) and in 10 children in the

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Table 5 – Indicators of basic microcirculation and amplitude-frequency spectrum of blood flow fluctuations in T1DM children in the area without arteriolo-venular anastomoses after 3 months of therapy with thioctic acid

Indicator	Main group (n = 32)			Control group (n = 32)		
	Initially	After 3 months	p	Initially	After 3 months	p
M	6.64 [4.37; 8.71]	6.21 [4.26; 7.68]	p=0.061	6.28 [4.28; 7.57]	6.01 [4.18; 8.11]*	p=0.234
s	0.845 [0.7; 0.96]	1.09 [0.82; 1.56]	p=0.035	0.86 [0.7; 0.97]	0.84 [0.66; 1.07]*	p=0.67
Cv	12.89 [9.81; 16.34]	27.06 [14.97; 28.71]	p=0.0004	14.29 [10.01; 19.39]	19.63 [9.72; 22.12]*	p=0.048
P_{eff}	1.43 [1.14; 2.91]	2.2 [1.58; 4.28]	p=0.034	1.51 [1.33; 2.06]	1.64 [1.18; 2.94]*	p=0.12
Ae	0.16 [0.12; 0.21]	0.3 [0.18; 0.42]	p=0.008	0.19 [0.16; 0.27]	0.21 [0.19; 0.37]*	p=0.07
ET	4.67 [3.38; 6.08]	4.22 [3.03; 5.1]	p=0.004	4.28 [3.21; 5.89]	4.18 [3.09; 4.99]*	p=0.37
Ae/3s	7.16 [5.52; 9.95]	7.91 [6.52; 10.99]	p=0.33	7.27 [5.32; 10.0]	7.65 [6.13; 9.97]*	p=0.28
Ae/M	2.61 [1.6; 4.18]	5.54 [2.31; 9.93]	p=0.019	3.41 [1.4; 5.11]	3.34 [1.82; 7.63]*	p=0.45
An	0.21 [0.16; 0.3]	0.28 [0.19; 0.6]	p=0.054	0.26 [0.21; 0.4]	0.24 [0.18; 0.34]*	p=0.23
NT	3.87 [2.87; 5.29]	3.19 [2.26; 4.37]	p=0.03	3.89 [2.6; 5.84]	4.01 [2.73; 6.09]*	p=0.048
An/3s	8.62 [6.81; 11.67]	8.55 [5.5; 12.82]	p=0.71	8.44 [6.74; 10.6]	8.69 [5.8; 11.67]*	p=0.54
An/M	3.62 [1.84; 6.88]	5.07 [3.8; 10.72]	p=0.07	3.04 [1.68; 7.34]	3.17 [1.75; 6.99]*	p=0.43
Am	0.23 [0.17; 0.34]	0.4 [0.24; 0.6]	p=0.09	0.32 [0.21; 0.38]	0.34 [0.17; 0.34]*	p=0.09
MT	3.43 [2.22; 5.09]	3.29 [2.19; 4.88]	p=0.234	3.2 [2.69; 4.58]	3.18 [2.39; 4.46]*	p=0.44
Am/3s	7.84 [5.97; 13.63]	9.19 [5.5; 14.96]	p=0.63	8.0 [6.03; 14.28]	8.14 [6.3; 13.44]*	p=0.37
Am/M	2.66 [1.95; 6.5]	7.45 [4.43; 11.58]	p=0.02	3.02 [2.09; 7.86]	3.24 [1.91; 8.03]*	p=0.56
Ar	0.22 [0.17; 0.38]	0.185 [0.13; 0.26]	p=0.04	0.28 [0.14; 0.42]	0.26 [0.15; 0.36]*	p=0.28
Ar/3s	6.72 [5.16; 10.43]	7.44 [6.57; 10.04]	p=0.12	6.84 [6.02; 9.89]	7.24 [5.75; 10.0]*	p=0.38
Ar/M	4.89 [3.14; 6.07]	3.3 [2.98; 3.52]	p=0.04	4.62 [3.23; 5.54]	4.97 [3.01; 5.87]*	p=0.65
Ac	0.26 [0.24; 0.51]	0.26 [0.22; 0.5]	p=0.89	0.24 [0.21; 0.49]	0.26 [0.22; 0.43]*	p=0.73
Ac/3s	14.02 [11.03; 18.29]	8.5 [6.72; 11.75]	p=0.0003	12.82 [12.43; 17.49]	10.42 [8.73; 15.27]**	p=0.02
Ar/M	5.62 [3.25; 8.94]	6.07 [3.56; 8.64]	p=0.36	5.17 [3.07; 7.36]	5.92 [3.34; 8.04]*	p=0.67
Ar/Ac	1.7 [1.22; 2.35]	1.26 [1.0; 1.64]	p=0.021	1.57 [1.17; 2.67]	1.63 [1.34; 2.12]*	p=0.19
SI	0.94 [0.88; 1.09]	0.92 [0.65; 1.17]	p=0.33	0.93 [0.75; 1.12]	0.96 [0.95; 1.28]*	p=0.07
IVT	0.66 [0.59; 0.85]	0.46 [0.38; 0.63]	p=0.003	0.57 [0.56; 0.64]	0.54 [0.48; 0.91]*	p=0.28

Note: M – mean perfusion; σ – standard amplitude deviation of blood flow fluctuations; Cv – coefficient of variation; P_{eff} – effective perfusion; Ae – fluctuations of neurogenic nature; ET – endothelial tone; An – neurogenic fluctuations; NT – neurogenic tone; Am – fluctuations of myogenic nature; MT – myogenic tone; Ar – fluctuations of respiratory nature; Ac – fluctuations of cardiac nature; A/M – amplitude of fluctuations relative to mean perfusion; A/3σ – amplitude of fluctuations relative to mean modulation of blood flow; SI – shunt index; IVT – intravascular tone; * – p<0.05 compared to the main group; ** – p>0.05 compared to the main group.

control group (31.25%). At the end of the study, resting tachycardia was observed only in 5 children in the main group (15.63%; p=0.08), and in 7 children in the control group (21.88%; p=0.4).

When performing a slow breathing test in the main group, there was an increase in the difference between the minimum and maximum heart rates (HRs) after a course of drug therapy with lipoic acid (initially it was 12.04±5.41, after 3 months – 17.18±2.14; p<0.001). In the control group, the increase was not statistically significant (initially – 13.14±4.75, after 3 months – 14.36±3.98; p=0.27).

During the Schelong test, there was a decrease in the blood pressure fall in the children treated with lipoic acid (initially it was 18.0±8.4, after 3 months – 11.45±7.8; p=0.002). According to D. Ewing, in the control group, there were no significant changes in the results of cardiovascular tests.

Since the largest number of parasympathetic and sympathetic fibers are located in the sinus and atrioventricular nodes of the heart conduction system, changes in the vegetative status significantly affect functioning of the cardiac conduction system, contribute to the development of atrioventricular tachycardia and life-threatening ventricular arrhythmia. The cause of a sudden cardiac death in diabetic patients may be a neuropathic prolongation of the QT interval, which is associated with changes in sympathetic and parasympathetic functions [1, 3, 4, 10, 22, 23, 33]. Therefore, the study of the heart rate variability, the measurement of the corrected QT interval and the dispersion of the QT interval are necessary methods in the diagnosis of autonomic neuropathy. In this study, a statistically significant decrease in the corrected QT interval in the main group was not obtained, however, a tendency to its normalization was revealed (initially, it was 0.452 [0.431; 0.467], after 3 months – 0.446 [0.425; 0.455], p = 0.063). During the initial examination, the heart rate variability was reduced in every third child in both groups (in the main group n=10, 31.25%; in the control group n=11, 34.4%). After 3 months, according to the Holter ECG monitoring, the heart rate variability was observed only in 6 children in

the main group (18.75%; p=0.09), in the control group – in 10 children (31.2%). After the treatment course in the main group, there was a trend towards normalization of temporary heart rate indicators (initially, pNN50% was 16 [8; 23], after 3 months it was 21 [19; 36], p=0.03; initially, SDNN was 128 [109; 166], after a month it was 164.5 [115; 172], p=0.048). In the control group, no statistically significant change in the indicators of time analysis was received. When assessing the spectral analysis of the heart rate variability in the children treated with lipoic acid, an increase in slow waves was revealed (initially, VLF were 2403 [1698; 3132], after 3 months – 3417 [2443; 4621], p = 0.01), in the control group there was a tendency to a decrease in waves in the slow range (initially, VLF were 2632 [1758; 3956], after 3 months – 2412 [1703; 3423], p=0.07).

Thus, the administration of lipoic acid improves a heart parasympathetic regulation in T1DM children. This is consistent with the results of a randomized study of vegetative-vascular regulation (VVR) in Korea, in which the authors found a positive trend in some parameters of VVR in DM patients who had been taking ALA 600 mg/day p. o. for the first 12 weeks and 1200 mg/day for the next 12 weeks. The DCAN study showed an improvement in the heart rate variability compared to placebo (p<0.05) in T2DM patients with impaired VVR who had been on ALC therapy at the dose of 800 mg/day [21].

In the groups under study, no statistically significant changes in the sympatho-parasympathetic balance index and daily blood pressure profile were found out.

Violation of microcirculation is the cause for nerve hypoxia, which is involved in the pathogenesis of diabetic neuropathy. It has been established that in DCAN patients, blood oxygen saturation and blood flow velocity in the vessels supplying the nerves, are reduced. These data indicate the importance of vascular factors along with hyperglycemia in the pathogenesis of neuropathy [3, 4, 7–9, 33, 35]. The prospective results of this microcirculation study are presented in Tables 4 and 5. Initially, the groups were comparable to each other (Table 4).

In the analysis of the basic microcirculation in the children of the studied groups, no pronounced change in the mean perfusion was detected, while a statistically significant increase in the coefficient of variation was observed, and in the main group, there was also an increase in the standard deviation of the amplitude of blood flow fluctuations (Table 5). These changes may be associated with an improved glycemic control, accompanied by a decrease in the glycemic variability during a day, which contributed to the functioning improvement of microvasculature regulatory systems. This assumption proves a significant increase in the effective perfusion index during treatment with lipoic acid in the main group (p=0.034).

When assessing fluctuations in the active tonus-forming range, in the children of the main group, a decrease in the endothelial-dependent component of the vascular tone (p=0.0004) was revealed. It was combined with an increase in the activity of fluctuations in the endothelial tonus-forming range (p=0.008) and an increase in the normalized amplitudes of the endothelial range relative to the mean perfusion (p=0.019). In the control group, no statistically significant difference in the amplitudes of fluctuations in the endothelial range was obtained, however, there was a tendency to increase them after improving glycemic control (p=0.07). In the main group, at the end of the treatment course, a decrease in the neurogenic component of vascular tone was observed (p=0.03), a tendency to an increase in the amplitudes of fluctuations in the active neurogenic range (p=0.54) was revealed. In the control group, an increase in the neurogenic component of the vascular tone was diagnosed (p=0.048), which indicates a gradual progression of neuropathy against the background of stable compensation of carbohydrate metabolism. The results obtained are confirmed by the DCCT study (The Diabetes Control and Complications Trial), which proved that after achieving a stable compensation of carbohydrate metabolism, the regression of diabetic neuropathy is doubtful [12].

When assessing the amplitude spectrum in the passive range against the background of therapy in the main group, a decrease in the amplitude of fluctuations in the respiratory range was observed (p=0.04).

The total indicator of intravascular tone on the background of the therapy in the main group significantly decreased (p=0.003). These changes may indicate the restoration of compensatory mechanisms due to an increase in the influence of active tone-forming factors and a decrease in intravascular tone. These trends indicate an improvement in microcirculation due to a decrease in the tone of metarteriols and precapillary sphincters in the microvasculature and, as a result, an improvement in the nutritional blood flow. Against the background of the therapy, the total indicator of the intravascular tone in the main group significantly decreased (p=0.003). These changes may indicate the restoration of compensatory mechanisms due to an increase in the influence of active tone-forming factors and a decrease in the intravascular tone. These trends indicate an improvement in microcirculation due to the decrease in the tone of metarteriols and precapillary sphincters in the microvasculature and, as a result, an improvement in the nutritional blood flow.

CONCLUSION

Thus, the inclusion of lipoic acid in the complex therapy of T1DM children, leads to an improvement in the course of the disease, contributes to the normalization of carbohydrate and lipid metabolism. The results obtained indicate the need to achieve and maintain optimal glycemic control with the absence of high glycemic variability, especially in the children with the first DCAN

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signs but this does not guarantee a complete regression of neuropathy manifestations.

To diagnose the initial manifestations of DCAN by studying the functional state of the microvasculature and its reserve capabilities, it is rational to operate with modern non-invasive LDF methods, which can be also used to control the ongoing therapy. The use of lipoic acid preparations at the daily dose of 600 mg for 3 months in the complex therapy in T1DM children with DCAN improves glycemic control, blood lipids, and also leads to an increase in vasomotor mechanisms of a tissue blood flow regulation due to an increase in endothelial and neurogenic activities accompanied by a decrease in intravascular tone and an increase in effective perfusion in tissues. The observed positive dynamics of D. Ewing cardiovascular tests, time (pNN50%, SDNN) and spectral parameters (VLF) of the heart rate variability during lipoic acid therapy can be explained, among other things, by the antioxidant and neuroprotective effects of the drug. The carried out study makes it possible to suggest that the use of thioctic acid at the dose of 600 mg/day for 3 months in the complex therapy of T1DM children at the preclinical stage of DCAN, leads to a regression of nerve fiber damage. The use of the LDF method for an early DCAN diagnosis and monitoring the effectiveness of therapy makes it possible to implement a personalized approach to the implementation of preventive treatment of T1DM children.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Natalya V. Malyuzhinskaya, Ivan N. Shishimorov, Olga V. Magnitskaya –concept and design of the study, literature analysis, interpretation and visualization of results, text writing; Olga V. Polyakova, Grigory V. Klitochenko, Irina V. Petrova, Svetlana A. Emelyanova – research methodology, interpretation and visualization of results, text writing; Ksenia V. Stepanenko, Anna P. Skiba – conducting functional tests and other studies, statistical processing of results, interpretation of results, text writing.

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