

The pathogenic treatment of diabetic peripheral neuropathy in patients with type 2 diabetes mellitus

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ABSTRACT

The study was conducted on 61 patients with Type 2 Diabetes Mellitus diagnosed the Distal Symmetrical Polyneuropathy (DSP). 31 patients from the study group were administered Thiogamma by i.v. route for first 3 weeks, followed by 600 mg orally for 4 weeks. 30 patients composed the control group. Follow-up was conducted in all patients. According to study data, Thiogamma therapy results in positive dynamics of DSP signs and symptoms, with improvement of reflexes and ENMG figures, indicating on better nerve function. Besides, the drug is positively effecting on carbohydrate metabolism. According to all above-mentioned, the Thiogamma could be widely used in treatment approach of the DPN in patients with Type 2 Diabetes Mellitus.

KEYWORDS: *type 2 diabetes mellitus, diabetic neuropathy, treatment, alpha-lipoic acid*

The Diabetic Neuropathy (DN) becomes the issue of increasing interest of world's endocrinologists in recent two decades, considering the fact that this is the most frequent and dangerous complication, leading to raising incidence of morbidity and mortality and to increasing of expenses in diabetes care [1,2]. The pharmaceutical mean with verified therapeutic effect in Diabetic Peripheral Neuropathy (DPN) does not exist till the present time. According to DCCT and UKPDS studies, the only method of treatment is regarded the strict control of glycaemia [3]. At the same time, according to some other studies (ALADIN, DECAN), the positive results were reached with alpha-lipoic acid in terms of pathogenic treatment approach.

The alpha-lipoic acid represents the metabolic cofactor of piruvate dehydrogenase complex and at the same time is the strong antioxidant. It improves the endoneural perfusion by inhibition of NO Synthetase suppression, preserving the neural tissue from ischemic damage; improves the nerve conduction velocity, normalizes the Glutathione level (Nagamatsu et. al, 1996; Androne et. al, 2000); inhibits the free radical dependent NF-kB activation; reduces the adhesive molecules activity (preserving the endothelial damage; Kunt et. al, 1999); preserves the neural damage by: restoring the level of spinal neuropeptides – Neuropeptide Y and Substance P; increasing the glucose endoneural diffusion (Low et. al, 1997); enhancing the activity of superoxid dismutase and superoxid catalase.

The aim of the study was the evaluation of action of "Thiogamma" (Wörwag Pharma, Germany) in patients with Type 2 Diabetes Mellitus with Distal Symmetric Polyneuropathy (DSP).

MATERIALS AND METHODS

61 patients of both sexes with Type 2 diabetes mellitus were evaluated. 31 of them consisted the study group and 30 – the control group. The clinical trial on Thiogamma was carried out at Georgian Diabetes Center in 2000-2004.

According to worked out protocol, all study group patients were administered Thiogamma during 7 weeks according to following scheme: 20 ml of Thiogamma i.v. in 200 ml 0.9 % saline for first 3 weeks, followed by 600 mg Thiogamma orally once a day for 4 weeks. The control group was matched to the study group considering the patients age, sex, diabetes duration and the grade of DN. The glucose level, blood pressure, lipid metabolism

and blood reological indicators were monitoring in both groups.

All patients successfully finished the clinical trial and got the total course of treatment with the Thiogamma. The patients were evaluated before, 3 weeks after the starting and at the end of the treatment after 7 weeks. The evaluation indicators were:

1. Patients complains;
2. Neurological tests: Vibration test (using a 128 Hz tuning fork), Pressure perception (using a Semmes-Weinstein 10 g monofilament), temperature sensitivity (using a dot), pain sensation (using a pin);
3. deep sensation using a tendon hammer (Achilles heel tendon reflex);
4. Evaluation of electoneuromiography data (with machine NOMAD).

The efficiency of Thiogamma was evaluated according to:

1. Dynamics of changes of scores according to Neuropathy Symptoms Score (NSS);
2. Neuropathy Deficit Scores (NDS), including the evaluation of neuropathy signs and reflexes;
3. Peripheral nerve functioning status.

The statistical analyses were carried out by the program "Biostatistics". The validity of difference was evaluated by the Student and Fisher's criteria. The difference was regarded statistically valid if $p < 0.05$.

RESULTS

The patients complains were estimated by their interviewing. The DSP clinical manifestation is presented in Tab.2.

As it is shown in the Tab.2, in 40-65 age adults group with DSP, the most frequent neuropathy complain is Paresthesia (93%), and with the decreasing incidence – the cold/warm feelings (64,5%), the pain (38,7%), the convulsion (6,4%) and the fatigue/weakness (12,8%). As for the reflexes, more frequently the diminished or even absence of reflexes were noted. At the same time the diminishing of ankle reflex (77,5%) was more frequent then of knee reflex (64,5%). The most frequently the temperature (100%), and then the vibration (96,7%) sensitivity is reduced.

After the 3 weeks of Thiogamma therapy, the patients are noting the disappearance of permanent and high-intensity nocturnal pains. They are stopping taking of analgesics after the 3-5 days of starting the treatment.

The results of conducted analyses revealed, that the neuropathy symptoms scores according to NSS,

significantly decreased after the conduction of i.v. course of therapy, the following oral administration of Thiogamma not only maintains the reached effect, but also ensures the positive dynamics of NSS scores.

Parameters	Study group	Control group
Number of patients	31	30
Sex (male/female)	14/17	12/18
Age (years)	56.48±8.89	57.8±8.36
BMI (kg/m ²)	31.95±6.099	30.53±4.918
Duration of diabetes (years)	8.806±6.46	7.1±5.095
HbA1c	7.69±0.7	7.39±0.75
Only Metformin	7	4
Sulfonylurea	2	4
Sulfonylurea and Metformin combination	11	10
Insulin therapy	11	9
Combined therapy (insulin+Sulfonylurea)	0	3
NSS	8.4±2.74	8.12±2.35
NDS	4.903±2.3	5.667±1.826

Tab.1 Distribution of patients according to clinical features.

Complains	n/%before/ after the treatment		Reflexes (decreased)	n/%before/ after the treatment	Sensation (abnormal)	n/%before/ after the treatment	
Pain	12/38.7%	1/3.2%	Ankle	24/77.4%	Pain hyposthesia	8/25.8%	6/19.4%
Convulsion	2/6.4%	0		16/51.6%	Vibration	30/96.7%	9/29%
Paresthesia	28/93%	2/6.4%	Knee	20/64.5%	Temperature	31/100%	11/35.5%
Fatigue/ weakness	4/12.8%	0		11/35.5%	Tactile examined with 10.0 g monofilament	3/9.7%	1/3.2%
Cold/warm feelings	20/64.5%	8/25.8%					

n – number of patients

Tab.2 DSP clinical manifestation in the study group.

	Points			p1-2	p2-3	p1-3
	At the beginning (1)	In 3 weeks (2)	In 7 weeks (3)			
NSS	8.4±2.74	4.12±2.35	1.48±2.67	<0,0001	<0,0001	<0,0001
NDS	4.903±2.3	2.75±2.7	1.935±2.34	=0.001	>0.05	<0.0001

Tab.3 The results of treatment after the 3 and 7 weeks of therapy.

The results of treatment after the 3 and 7 weeks of therapy are presented in Tab.3.

The carried out analyses has shown the statistically valid reducing of scores of Diabetic Polyneuropathy symptoms according to NSS during the conduction of the study. After the 3 weeks of treatment, the reducing for more then 1 score was noted in 87%, and after the 7 weeks – in 100%. Also, it should be noted that in 12 patients with awakening pain at night, only 4 still had this symptom after 3 weeks of therapy, and only 1 – after the 7 weeks of treatment. According to NDS, the statistically valid reducing of neuropathy scores was evident, especially after the i.v therapy.

Thiogamma therapy leads to statistically valid improvement of vibration sensation in distal part of lower extremities.

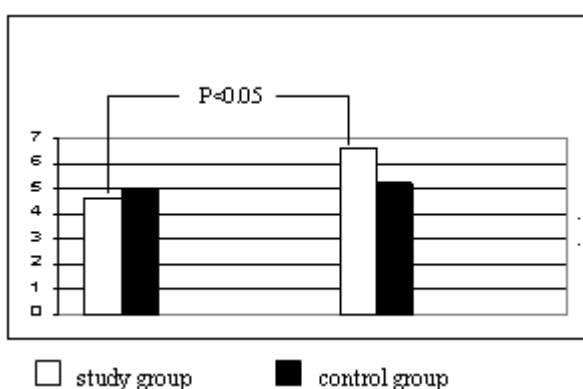


Fig.1 Compare of the vibration sensation improvement in study and control groups.

As it is shown in the Table 5, among the ENMG parameters, most frequent is the M-indicator's amplitude reducing in motor nerve and decreasing of nerve conduction velocity in sensor nerve. Other parameters of deviation from the normal level is rare.

The received results indicate on the positive dynamics of clinical parameters of DSP with the Thiogamma therapy.

As this is shown in the Tab.2, all patients noted the full regression of their complains after the completion of the therapy. The vibration sensation was normalized in 21 (70%) patients; the pain sensation became normal in all patients, the tactile perception recovered in 2 (67%) patients. The ankle and knee reflexes recovered in 9 (45%) and 8 (37. 5%) patients accordingly. According to ENMG data, the raising tendency of M-indicator's amplitude was found in motor nerve, and the initially low M-indicator's amplitude increased in 15 cases. The increased tendency of nerve conduction velocity was noted. In 69 % patients with reduced nerve conduction velocity, this indicator was not improved. The significant positive dynamics of AP mean level was not found in sensor nerve.

During the conduction of therapy, the HbA1c level significantly reduced in study group (from 7.69 ± 0.73 to $6.23 \pm 0.8\%$) compared to control group (from 7.39 ± 0.75 to $6.59 \pm 0.85\%$), indicating on Thiogamma positive effects on carbohydrate metabolism. The drug is not effecting the blood and urine general indicators.

The local and general signs of Thiogamma intolerance, as well as side effects were not noted. It should be stressed, that the decreasing of glycemia level by 30% after the Thiogamma i.v. administration was making the necessity of getting the additional meals before the infusion. The received results are indicating, that Thiogamma i.v. and then oral administration is significantly reducing the clinical manifestation of DN. The remarkable positive dynamics of DSP signs and symptoms are evident, with improvement of reflexes and ENMG figures, indicating on better nerve function. Thiogamma therapy improves the general status of patients, they are feeling better (the symptoms are disappearing and the sensation is improving), their working ability and the tolerance to the physical activity is raising, accordingly the quality of life is also improving. According to all above-mentioned, Thiogamma could be recommended for treatment of peripheral polyneuropathy in Type 2 Diabetes Mellitus.

Visits	The mean indicator of 3 measurements (M±m)			
	The proximal joint level of big finger of the foot		Medial Maleolus level	
	Right	Left	Right	Left
1	4.6±1.6	4.41±2.089	5.3±1.7	5.37±1.73
2	5.58±1.7	5.37±1.3	6.02±1.24	6.03±1.4
3	6.69±1.28	6.58±1.35	6.17±1.46	6.1±1.506
p1-2	=0.023	=0.034	=0.062	=0.104
p2-3	=0.005	<0.0001	=0.664	=0.850
p1-3	<0.0001	<0.0001	=0.035	=0.081

Tab.4 Indices of vibration sensation.

Indicator	Normal level	M±m	Abnormal n/%
N. PERONEUS (N=31)			
M-indicator's amplitude	N>3,5MV	3.55±0.04	22 (70%)
Impulse conduction velocity	N>40M/S	47.15±3.0	6 (20%)
Residual latency	N<3M/S	2.14±0.18	2 (5%)
N. SURALIS (N=31)			
Action potential	N>5MV	8.01±1.1	12 (38.7%)
Impulse conduction velocity	N>40M/S	50.1±2.4	4 (12.9%)

Tab.5 Electroneuromiography (ENMG) data.**REFERENCES:**

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Патогенетическое лечение диабетической периферийной нейропатии у больных сахарным диабетом типа 2

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РЕЗЮМЕ

Обследован 61 больной сахарным диабетом типа 2 с дистальной симметричной полинейропатией. Препарат тиогамма (альфа-липоевая кислота) сначала в виде внутривенной инфузии (3 недели), а затем перорально в виде таблетированной формы препарата (600 мг) в течение 4 недель получал 31 больной основной и 30 пациентов контрольной группы. Наблюдение проводилось в динамике. Лечение препаратом привело к положительной динамике симптомов ДПН в виде оживления рефлексов, улучшения электронейромиографических показателей, свидетельствуя об улучшении функции нервных волокон. Препарат оказывает положительное влияние на углеводный обмен. По результатам исследования препарат тиогамма можно широко использовать в диабетологии.

Ключевые слова: сахарный диабет типа 2, диабетическая нейропатия, лечение, альфа-липоевая кислота