THE ROLE OF α-LIPOIC ACID IN DIABETIC POLYNEUROPATHY TREATMENT

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Abstract

Diabetic neuropathy represents late diabetes complications, and diabetes duration and long-term hyperglycemia are the main reasons for polyneuropathy. The goal was to estimate the effects of α-lipoic acid on symptoms of diabetic neuropathy after 600 mg i.v. for 3 weeks and 3 months of 300-600 mg of α-lipoic acid per os. This study has been designed as a multicentric, in 5-centers in B&H, carried out by 5 physicians with 20 diabetic patients each. Following parameters were monitored in 100 diabetics suffering from Type 1 and Type 2 diabetes, both men and women: diabetes duration, diabetes therapy, duration of polyneuropathy symptoms, height, weight, BMI (body mass index), subjective assessment of patients, objective examinations of physicians and subjective assessment of physicians. 100 diabetics, average age 61,36; oldest 79, youngest 40, suffered from diabetes in average 11,9 years. There were 35 men and 65 women, 16 with Type 1 and 80 with Type 2 diabetes, while 4 patients were not classified. 69 were having insulin therapy and 31 oral hypoglicemics. Shortest diabetic status was less than a year, and longest was 28 years. Average duration of polyneuropathic symptoms was 3,02 years, shortest was less than a year, and the longest was 15 years. Average height was 1,70 m, average weight 76,13 kg, and average BMI 26,51 kg/m2. Significant statistic differences in improvement were recorded (P>0,05) according to Fridman's test for repeated measurements compared to initial findings in assessments: sensory symptoms of polyneuropathy, pain sensations as polyneuropathy symptoms, total score of polyneuropathy symptoms, subjective assessment of patients, subjective findings of physicians, and significant differences were not find (P>0,05) in autonomous and motoric neuropathy. Based on the conducted study, we have concluded that the application of α-lipoic acid during 3 months has helped to decrease the symptoms of diabetic neuropathy and in only one case out of 100 included patients there was no subjective improvement after drug application.

KEY WORDS: diabetes mellitus, polyneuropathy, α-lipoic acid

Introduction

Diabetic neuropathy represents late micro vascular diabetes complications and it is manifested by slower conduction of nerve impulse and axonal transport damage and nerve cell structure damage. Diabetes duration and long-term hyperglycemia are the main reasons for late diabetes complications and polyneuropathy (1,2). Around 12% of diabetics have already some of polyneuropathy symptoms in the moment when the disease is diagnosed, and according to some epidemiologic researches, 50-80% of diabetics have clinical signs of diabetic neuropathy in later phase of the disease. Different symptoms occur depending on place of the changes happening. Dystal sensory and motoric polyneuropathy are most common. Main symptoms are: paresthesia, night pain in muscles, spasms and others (3, 4). The most common form of diabetic neuropathy is symmetric polyneuropathy and it is manifested through: sensitivity loss on symmetric dystal part of lower limbs, loss of reflexes in feet, balance disorder; paresthesia is manifested through sense of numbness, loss of sense of touch, of pain, "burning sensation" or "tingling" which starts in feet and then spreads up to upper part of legs. Neuropathic pain usually affects lower limbs, present when resting and increases at night. Diabetic neuropathy is divided into: a) Dystal polyneuropathy (sensory- motoric, mostly sensory and mostly motoric), b) Proximal polyneuropathy, c) Autonomous neuropathy (loss of hypoglycemia warning signs, change in pupilary function of function of lachrymal gland, cardiovascular and lung disturbances, thermoregulatory disturbances, gastrointestinal disturbances, genitourinary disturbances). In order to set up diagnosis, beside history data and clinical picture, one must also undergo electromyography (EMG) of limbs which shows the speed of nerves conduction (5,6,7).

Materials and Methods

This study has been designed as a multicentric, in 5-centers in B&H, carried out by 5 physicians with 20 diabetic patients each. Following parameters were monitored in 100 diabetics suffering from Type 1 and Type 2 diabetes, both men and women: diabetes duration, diabetes therapy, duration of polyneuropathy symptoms, heights, weight, BMI (body mass index). Following symptoms of polyneuropathy were monitored: autonomous, sensory, motoric, pain sensation, total sum of symptoms

All above said symptoms have been graded at the beginning of the research:

No symptoms – 0; Mild – 1; Moderate -2; Severe -3; Total sum of all symptoms

During the follow-ups, once in 15 days, patients subjectively assessed their condition as:

Worsening -1;Unchanged -2; Moderate improvement -3; Significant improvement -4

During the follow-ups, once in 15 days, based in subjective assessment of symptoms and objective examinations, the physicians assessed the condition as:

Worsening -1; Unchanged -2; Moderate improvement -3; Significant improvement -4

Administering protocol was same for all patients: 3 weeks, from Monday to Friday, they received 600 mg i.v. of α-lipoic acid and during the weekend they took 2x1 tablets of 300 mg. In next 3 months, the patients took 2x1 or 1x1 tablets of 300 mg.

Results

100 diabetics, average age 61,36 years, oldest 79, youngest 40, suffered from diabetes in average 11,9 years. There were 35 men and 65 women, 16 with Type 1 and 80 with Type 2 diabetes, while 4 patients were not classified. 69 were having insulin therapy and 31 oral hypoglicemics. Shortest diabetic status was less than a year, and longest was 28 years. Average duration of polyneuropathic symptoms was 3,02 years, shortest was less than a year, and the longest was 15 years. Average height was 1,70 m, average weight 76,13 kg, and average BMI 26,51 kg/m2. Table 1. shows the symptoms of autonomous polyneuropathy at the beginning of the research and during 7 follow-ups, done in descriptive manner.

According to Fridman's test for repeated measurements there were no significant statistic differences in initial findings, follow-ups and last finding of changes with respect to signs of autonomous polyneuropathy.

Table 2. shows the symptoms of sensory polyneuropathy at the beginning of the research and during 7 follow-ups, done in descriptive manner.

According to Fridman's test for repeated measurements there were significant statistic differences in initial findings, follow-ups and last finding of changes, where $p<0,05$ since the fourth follow-up with respect to signs of sensory polyneuropathy. Table 3. shows the symptoms of motoric polyneuropathy at the beginning of the research and during 7 follow-ups, done in descriptive manner. According to Fridman's test for repeated measurements there were no significant statistic differences in

Autonom. polyneur.	Number of patients	Average value	Standard deviation	Max. points	Min. points	Median points
Initial find.	100	0,97	0,88	3	0	1
1. follow-up	100	0,83	0,83	3	0	1
2. follow-up	100	0,91	0,88	3	0	1
3. follow-up	100	0,51	0,71	3	0	0
4. follow-up	100	0,54	0,70	3	0	0
5. follow-up	100	0,43	0,60	2	0	0
6. follow-up	100	0,60	0,71	2	0	0
Final find.	100	0,60	0,71	2	0	0

TABLE 1. Evaluation the symptoms of autonomous polyneuropathy

Sensory polyneur.	Number of patients	Average value	Standard-deviation	Max. points	Min. points	Median points
Initial find.	100	1,84	0,67	3	0	2
1. follow-up	100	1,7	0,64	3	0	2
2. follow-up	100	1,51	0,66	3	0	1,5
3. follow-up	100	1,26	0,68	3	0	1
4. follow-up	**100**	**1,20**	**0,60**	**3**	**0**	**1**
5. follow-up	**100**	**1,07**	**0,61**	**2**	**0**	**1**
6. follow-up	**100**	**0,99**	**0,61**	**2**	**0**	**1**
Final find	**100**	**0,99**	**0,61**	**2**	**0**	**0**

TABLE 2. Evaluation the symptoms of sensory polyneuropathy

Motoric polyneur.	Number of patients	Average value	Standard deviation	Max. points	Min. points	Median points
Initial find.	100	1,32	0,78	3	0	1
1. follow-up	100	1,24	0,77	3	0	1
2. follow-up	100	1,18	0,72	3	0	1
3. follow-up	100	1,12	0,75	3	0	1
4. follow-up	100	1,05	0,66	2	0	1
5. follow-up	100	1,00	0,68	2	0	1
6. follow-up	100	0,94	0,58	2	0	1
Final find.	100	0,94	0,58	2	0	1

TABLE 3. Evaluation the symptoms of motoric polyneuropathy

Pain sensation	Number of patients	Average value	Standard-deviation	Max. points	Min. points	Median points
Initial find.	100	1,98	0,73	3	0	2
1. follow-up	100	1,84	0,77	3	0	2
2. follow-up	100	1,41	0,69	3	0	1
3. follow-up	100	1,11	0,7	3	0	1
4. follow-up	**100**	**0,95**	**0,62**	**2**	**0**	**1**
5. follow-up	**100**	**0,79**	**0,64**	**2**	**0**	**1**
6. follow-up	**100**	**0,67**	**0,61**	**2**	**0**	**1**
Final find.	**100**	**0,67**	**0,63**	**2**	**0**	**1**

TABLE 4. Evaluation the symptoms of pain sensation as sign of polyneuropthy

initial findings, follow-ups and last finding of changes with respect to signs of motoric polyneuropathy. Table 4. shows the symptoms of pain sensation as a sign of polyneuropathy at the beginning of the research and during 7 follow-ups, done in descriptive manner.

According to Fridman's test for repeated measurements there were significant statistic differences in initial findings, follow-ups and last finding of changes, where $p<0,05$ since the fourth follow-up with respect to pain sensation as a symptom of polyneuropathy. Table 5. shows the sum findings polyneuropathy signs (autonomous, sensory, motoric and pain sensation) at the beginning of the research and during 7 follow-ups, done in descriptive manner. According to Fridman's test for repeated measurements there were significant statistic differences in initial findings, follow-ups and last finding of changes, where $p<0,05$ since the fourth follow-up when all symptoms of polyneuropathy have been summed up.

Sum findings	Number of patients	Average value	Standard-deviation	Max. points	Min. points	Median points
Initial find.	100	5,23	2,47	11	1	5,5
1. follow-up	100	4,27	2,30	11	1	5
2. follow-up	100	4,22	2,29	11	0	4
3. follow-up	100	3,20	2,32	11	0	4
4. follow-up	**100**	**2,50**	**2,24**	**9**	**0**	**2**
5. follow-up	**100**	**2,06**	**2,05**	**7**	**0**	**1,5**
6. follow-up	**100**	**2,38**	**2,01**	**7**	**0**	**2**
Final find.	**100**	**2,41**	**2,05**	**7**	**0**	**2**

TABLE 5. Evaluation the sum findings polyneuropathy signs

Subject. asses. patients	Number of patients	Average value	Standard deviation	Max. points	Min. points	Median points
Initial find.	100	4,92	0,27	5	4	5
1. follow-up	100	4,28	0,99	5	2	5
2. follow-up	100	3,32	0,79	5	2	3
3. follow-up	**100**	**2,96**	**0,58**	**5**	**2**	**3**
4. follow-up	**100**	**3,00**	**0,65**	**5**	**2**	**3**
5. follow-up	**100**	**2,87**	**0,52**	**4**	**2**	**3**
6. follow-up	**100**	**2,68**	**0,51**	**4**	**2**	**2**
Final find.	**100**	**2,55**	**0,52**	**4**	**2**	**2**

TABLE 6. Evaluation the subjective assessment of patients on severity of polyneuropathy signs

Physic. findings	Number of patients	Average value	Standard deviation	Max. points	Min. points	Median points
Initial find.	100	4,81	0,39	5	4	5
1. follow-up	100	3,88	0,83	5	2	3
2. follow-up	**100**	**3,49**	**0,85**	**5**	**2**	**3**
3. follow-up	**100**	**2,93**	**0,55**	**5**	**2**	**3**
4. follow-up	**100**	**2,96**	**0,43**	**5**	**2**	**3**
5. follow-up	**100**	**2,84**	**0,36**	**3**	**2**	**3**
6. follow-up	**100**	**2,84**	**0,36**	**3**	**2**	**3**
Final find.	**100**	**2,66**	**0,47**	**3**	**2**	**2**

TABLE 7. Evaluation the assessment of physicians on severity of polyneuropathy signs

Table 6. shows the subjective assessment of patients on severity of polyneuropathy signs (autonomous, sensory, motoric and pain sensation) at the beginning of the research and during 7 follow-ups, done in descriptive manner.

According to Fridman's test for repeated measurements there were significant statistic differences in initial findings, follow-ups and last finding of changes, where $p<0,05$ since the third follow-up when patients expressed on changes in symptoms of polyneuropathy. Table 7. shows the assessment of physicians on severity of polyneuropathy signs (autonomous, sensory, motoric and pain sensation) based on the objective examination and subjective assessments at the beginning of the research and during 7 follow-ups, done in descriptive manner. According to Fridman's test for repeated measurements there were significant statistic differences in initial findings, follow-ups and last finding of changes, where $p<0,05$ since the second follow-up when physicians expressed the changes in symptoms of polyneuropathy.

Discussion

Diabetic neuropathy represents late micro vascular diabetes complications and it is manifested by slower conduction of nerve impulse and axonal transport damage and nerve cell structure damage. Diabetes duration and long-term hyperglycemia are the main reasons for late diabetes complications and polyneuropathy. Polyneuropathy and its symptoms are very uncomfortable for patients and can lead to severe disability, which represents huge medical, social and economic problem (8,9). Consequences of late diabetes complications are much harder to treat than diabetes itself. This refers to polyneuropathy as well. Products of α-lipoic acid are used lately to treat diabetic polyneuropathy. Studies done throughout the world showed the success of α-lipoic acid (10). ALADIN I study was designed so to show the effects of α-lipoic acid after short term ap-

plication of 600-1200 mg i.v. during 3 weeks. ALADIN II study showed the effects of α-lipoic acid after per os. long term administration as to better conductivity of nerve impulse. ALADIN III study showed the effects of long term per os. therapy with 600 mg of α-lipoic acid, after 3 weeks of 600 mg i.v. Our study was also designed as ALADIN III study, which showed the best results in the world, and we wanted to present the effects of α-lipoic acid on our patients (11,12).

Conclusion

Based on our research, we came to the following conclusions:
1. There were significant statistic differences (P<0,05) compared to initial findings when assessed: sensory polyneuropathy symptoms; pain sensations as polyneuropathy symptoms; total score of polyneuropathy symptoms;subjective assessments of patients; subjective findings of physicians
2. There were no differences (P>0,05) between the initial findings and final finding in autonomous polyneuropathy symptoms and motoric polyneuropathy symptoms, although certain improvements were recorded also in these assessments. A possible reason for such result is a lack of polyneuropathy symptoms in this group of patients referring to autonomous and motoric symptoms and in that case we cannot expect improvements in that sense.
3. Based on our research, we have concluded that the application of α-lipoic acid during 3 months has helped to decrease the symptoms of diabetic polyneuropathy and that in only one case out of 100 included patients there was no subjective improvement after drug application.

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