Original Paper

Classical Therapies Versus Combined Therapies in Diabetic Neuropathy

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ABSTRACT: The aim of our study was to evaluate the classical therapies represented by adequate glycemic control and lifestyle changes versus classical therapies combined with new antioxidant therapies in patients with diabetic neuropathy. We conducted an observational, prospective study, between October 2017 and December 2019, which included a number of 188 patients suffering from diabetic neuropathy. In order to evaluate the response to the therapeutic protocol, we used the MNSI (Michigan neuropathy screening instrument). Responder group was defined as a decrease in MNSI (<7) from baseline to one year. According to this 34.04% (n=64) of patients were responders to classical therapy while a higher number of patients responded to combined therapy (n=73, representing 38.83%). In the group of responders, the subgroups that predicted the prevention of MNSI increase (decrease in the impact of diabetic neuropathy) in the group treated with combined therapy compared to classical therapy, related to clinicopathological features, after one year included: gender female (p=0.0415), body mass index <30kg/m2 (p=0.0335), absence of cardiovascular disease (p=0.0006) and absence of dyslipidemia (p=0.0288). In conclusion, we demonstrated an increased response to combined therapy after one year of treatment. Thus, combined therapy is an alternative for reducing side effects and for increasing efficiency.

KEYWORDS: *Antioxidant therapy, glycemic control, lifestyle changes, diabetic neuropathy.*

Introduction

Representing one of the most worrying public health problems nowadays, diabetes, together with its complication, diabetic neuropathy have both an increasing incidence and prevalence worldwide [1].

There are clinical studies that describe the presence of diabetic neuropathy in both patients suffering from type 1 diabetes and in patients suffering from type 2 diabetes [1].

It has been concluded that this pathological condition has a higher incidence in patients with type 2 diabetes compared to patients with type 1 diabetes (6100 cases compared to 2800 cases reported per 100,000 persons/year) [2-5].

On the other hand, when we refer to the prevalence of this pathological condition, it was found that both patients suffering from type 1 diabetes and patients suffering from type 2 diabetes have appropriate values (11-50% for type 1 diabetes [6-7] and 8-51% for type 2 diabetes [1,8].

When asymptomatic neuropathy is also included in the notion of diabetic neuropathy the prevalence of this pathological condition is higher in patients with type 1 diabetes compared to patients with type 2 diabetes (54% versus 45%) [1,7].

It has also been shown that the prevalence of diabetic neuropathy increases as diabetes progresses [9].

Diabetic neuropathy is the most common complication of diabetes, but, fortunately, not the most serious, it is caused by peripheral nerve damage, which has a negative impact on patients' lives due to clinical symptoms, the most annoying of which is, by far, the neuropathic pain [2].

This pathological condition is associated with chronic hyperglycemia, which is very common in both types of diabetes, with damage of small blood vessels and, nevertheless, with various metabolic abnormalities, such as the accumulation of reactive oxygen species and increased oxidative stress, which, in turn, plays an important role in affecting the autonomic nervous system and sensory function [1,2].

Regarding the treatment, there is the classical therapy, which is strictly directed on clinical symptomatology, but, more and more clinicians, have observed the benefits of pathogenic treatment with B vitamins and alpha-thioctic acid, treatment, which is directed on the pathophysiological causes, thus, improving motor, sensory and autonomous symptoms [5].

The aim of our study was to evaluate the classical therapies represented by adequate glycemic control and lifestyle changes versus classical therapies combined with new antioxidant therapies in patients with diabetic neuropathy.

Material and Methods

Study type and Methods

We conducted an observational, prospective study, between October 2017 and December 2019, which included a number of 188 patients suffering from diabetic neuropathy.

In order to avoid bias patients were consecutively included in the study.

These patients were hospitalized and monitored in the Diabetology Department of the Emergency County Hospital of Slatina, Romania.

Approvals were obtained from both the Ethics Committee of University of Medicine and Pharmacy of Craiova and, also, from the hospital where the patients were hospitalized.

The present study was based on the original cohort, that was received either classical therapy (adequate glycemic control together with lifestyle changes and it included a number of 95 patients) or combined therapy (classical therapy plus antioxidant therapy and it included a number of 93 patients).

The combined antioxidant therapy consisted of was vitamin B complex (Benfotiamine-B1 and Pyridoxine-B6 as Milgamma 100mg, Germany) and film-coated tablets containing 600mg of alpha thioctic acid, it was administered according to the protocols previously described [9,10] for a period of one year.

It should be mentioned that intravenous therapy was initially applied for 10 days according to the protocol previously described [9].

The inclusion criteria in the study were represented by: diabetic neuropathy, diabetes, patient acceptance to participate in the study and in the follow-up.

The exclusion criteria were: peripheral neuropathies with other etiology besides diabetes (autoimmune diseases, severe hypothyroidism, renal dysfunction, paraneoplastic diseases, immunosuppressive medication, ethanol consumption, etc.), patients' refusal to participate in the study, the presence of grade III or morbid obesity and pregnancy.

When included in the study, patients were evaluated, then, they were again evaluated after finishing the ten days injectable treatment, then at three-month interval for at least one year and then at one year.

In order to evaluate the response to the therapeutic protocol, we used the MNSI (Michigan neuropathy screening instrument) [11,12].

The MNSI calculation is based on the clinical examination, which is usually performed by the diabetologist or neurologist and, also, on the evaluation of the patient, which is performed by completing a questionnaire with 15 questions. MNSI was translated into Romanian language, in order to make it easy for patients to complete the questionnaire. The MNSI tool is shown in Figure 1.

The protocol was used according to previously published descriptions [1,11-13].

We considered a pathological value of MNSI ≥7 as non-responders [12].

Responder group was defined as a decrease in MNSI (MNSI <7) from baseline to one year.

	Michigan neuropathy screening instrument (MNSI)
1.	Are your legs and/or feet numb?
2.	Do you ever have any burning pain in your legs and/or feet?
3.	Are your feet too sensitive to touch?
4.	Do you get muscle cramps in your legs and/or feet?
5.	Do you ever have any prickling feelings in your legs or feet?
6.	Does it hurt when the bed covers touch your skin?
7.	When you get into the tub or shower, are you able to tell the hot water from the cold water?
8.	Have you ever had an open sore on your foot? If yes, do you have one now?
9.	Has your doctor ever told you that you have diabetic neuropathy?
10.	Do you feel weak all over most of the time?
11.	Are your symptoms worse at night?
12.	Do your legs hurt when you walk?
13.	Are you able to sense your feet when you walk?
14.	Is the skin on your feet so dry that it cracks open?
15.	Have you ever had an amputation?

Figure 1. Michigan neuropathy screening instrument (MNSI).

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The influence of clinicopathological features on the efficacy of combined therapy versus classical therapy was assessed in subgroups of patients stratified by body mass index (BMI, <30kg/m^2 or> 30kg/m^2), age (<60 years or ≥60 years), gender (female or male), diabetes type (1 or 2), diabetes duration (<10 years or ≥10 years), glycated hemoglobin (HbA1C-%<7 or ≥7), the use of oral antidiabetic drugs (yes or no), insulin treatment (yes or no), systolic blood pressure (SBP, <140mmHg or ≥140mmHg), diastolic blood pressure (DBP, <90mmHg or ≥90 mmHg), presence of cardiovascular disease (CVD, yes or no), neuropathy duration (<3 or ≥3 years), presence of nephropathy (yes or no), presence of retinopathy (yes or no), presence of dyslipidemia (yes or no) and smoking (yes or no).

Statistical Analysis

All data were analyzed with the statistical package GraphPad (version 8, GraphPad Software, La Jolla, CA, USA).

All results were recorded as mean and standard deviation for continuous variables and as absolute number and percentage value (%) for qualitative variables.

To compare the mean of two groups we used the t-student test.

Then, we analyzed the effects of the two therapies by calculating the odds ratio (OR) with 95% confidence interval (CI) by using Baptista-Pike method.

To analyze the statistical difference in the case of qualitative data we used the Fisher or Chi-square test.

In all cases the value of P <0.05 was considered statistically significant.

Table 1. Clinicopathological features of the subgroups at baseline.

	Classical therapy (n=95)	Combined therapy (n=93)	P value
Age (years)	59.60±11.21	60.40±10.52	0.570#
Gender: female	43 (22.87%)	40 (21.28%)	0.559*
Gender: male	59 (31.38%)	46 (24.47%)	
Body mas index (kg/m²)	32.47±7.81	33.50±8.72	0.786#
Type 1 diabetes	43 (22.87%)	42 (22.34%)	0.558*
Type 2 diabetes	57 (30.32%)	46 (24.47%)	
Diabetes duration (years)	10.4±4.56	11.1±5.34	0.322#
HbA1C (%)	7.73±4.80	7.45±5.21	0.845#
Oral antidiabetic drugs	30 (15.96%)	32 (17.02%)	0.750*
Insulin treatment	70 (36.17%)	66 (430.85%)	0.777*
Systolic blood pressure: (140mmHg)	139±55	133±49	0.450#
Diastolic blood pressure: (mmHg)	83±37	81±28	0.341#
Cardiovascular disease	43 (22.63%)	47 (24.74%)	0.686*
Neuropathy duration (years)	4.2±2.7	3.9±2.4	0.120#
Nephropathy	23 (12.23%)	26 (13.83%)	0.733*
Retinopathy	19 (10.11%)	21 (11.17%)	0.769*
Dyslipidemia	81 (43.09%)	69 (36.70%)	0.473*
Active smokers	69 (36.70%)	61 (32.45 %)	0.999*
These data are reported as absolute number and percentage value (%) for qualitative variables and as mean±SD for continuous variables. #t test. * Fisher test.			

Results

The outcome measures and clinicopathological features at baseline in both groups are shown in Table 1.

Depending on the MNSI score at one year after the inclusion in the study, each patient was included in the responders group if the MNSI dropped below 7 or in the non-responders group if the MNSI did not drop below 7.

According to this 34.04% (n=64) of patients were responders to classical therapy while 16.49% (n=31) of patients were non-responders to classical therapy.

On the other hand, a higher number of patients responded to combined therapy (n=73, representing 38.83%) and only 21.51% (n=20) were non-responders to combined therapy (p=0.101, OR=0.56, 95% CI 0.2967 to 1.106 and reciprocal OR=1.76, 95% CI 0.9206 to 3.370).

These data are shown in Figure 2.

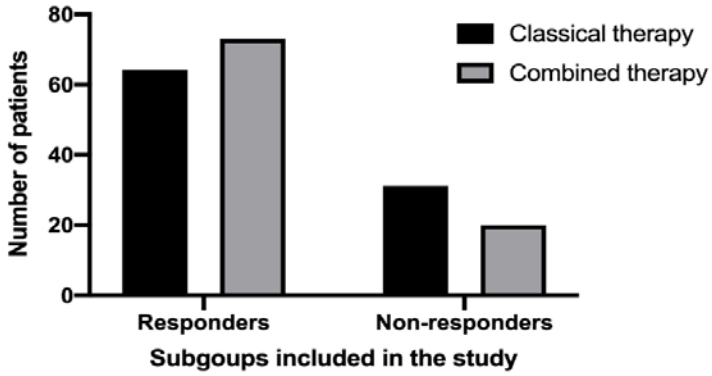

Figure 2. Responders and non-responders at one-year follow-up depending on the applied therapy.

In the group of responders, the subgroups that predicted the prevention of MNSI increase (decrease in the impact of diabetic neuropathy) in the group treated with combined therapy compared to classic therapy, related to clinicopathological features, after one year included: gender female (p=0.0415, OR=3,167, 95% CI 1,102 to 8,138), body mass index <30kg/m^2 (p=0.0335, OR=2,762, 95% CI=0,903 to 5,601), absence of cardiovascular disease (p=0.006, OR=3,167, 95% CI 1,367 to 6,871) and absence of dyslipidemia (p=0.0288, OR=2,917, 95% CI=1,880 to 6,730).

Patients with these characteristics were responders to combined therapy versus classical therapy.

Figure 3A shows the forest plot with OR and 95% CI for responders to combined therapy versus classical therapy related to clinicopathological features.

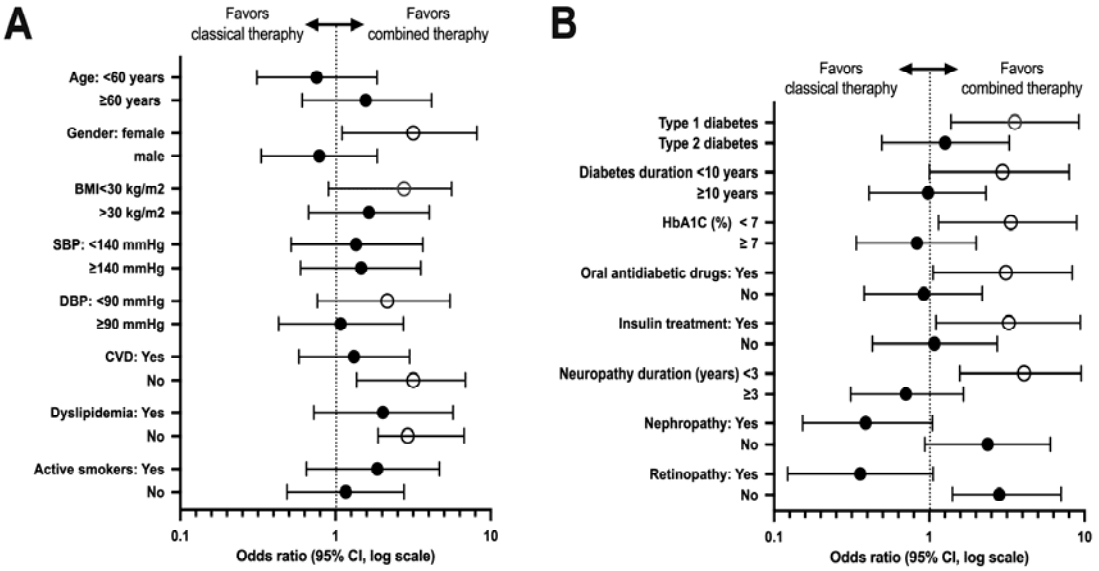

Figure 3. Odds ratios (OR) with 95% confidence intervals (log scale) for baseline predictors of improvement of MNSI score (responders) related to clinicopathological features (A) and to diabetes mellitus and neuropathy (B) in the classical therapy group compared to combined therapy group over one year. Open circles signify the statistically significant difference (p<0.05).

Figure 3B shows the forest plot with OR and 95% CI for responders to combined therapy versus classical therapy related to diabetes mellitus and neuropathy.

In this case, significant improvements of the MNSI score (in the responders) were observed in the combined therapy group compared to classical therapy after one year for baseline subgroups with type 1 diabetes (p=0.0152, OR=3,556, 95% CI 1,379 to 9,187), diabetes duration <10 years (p=0.0402, OR=2,961, 95% CI 1,002 to 7,957), HbA1C <7% (p=0.0331,

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OR=3,351, 95% CI 1,146 to 8,906), patients with oral antidiabetic drugs (p=0.0358, OR=3,117, 95% CI 1,058 to 8,336), patients with insulin treatment (p=0.0368, OR=3,250, 95% CI 1,104 to 9,397) and neuropathy duration <3 years (p=0.0041, OR=5,388, 95% CI 1,57 to 15,53).

Discussion

Diabetes mellitus together with diabetic neuropathy is today a worrying global health problem [14], on the one hand, because the number of people diagnosed with diabetes that develop diabetic neuropathy has significant increased and, on the other hand, patients diagnosed with diabetic neuropathy often complain of severe neuropathic pain [1].

According to current diagnostic and treatment guidelines of diabetic neuropathy, symptomatic treatment, whose purpose is to reduce neuropathic pain, without having any effect on the cause, along with pathogenic treatment, whose purpose is to slow down or even stop the evolution of neuropathic disease, are the only accepted therapeutic options. Although currently symptomatic treatment, including drugs such as duloxetine, which improves pain-inhibiting downstream pathways or drugs such as pregabalin, and gabapentin, which have a rapid effect on pain because they reduce central hyperexcitability, are considered by clinicians first-line drugs, more and more studies highlight the beneficial effects of pathogenic treatments [15].

The pathogenic treatment, which is mainly based on the use of benfotiamine and alpha thioctic acid, the first one blocks the main pathways of hyperglycemia and the alpha thioctic acid helps improving microcirculation by its antioxidant and anti-inflammatory roles, has proven its effectiveness in many clinical trials [11].

Thus, the most important substances used in the treatment of diabetic neuropathy are alpha thioctic acid, benfotiamine, duloxetine, pregabalin and gabapentin [1,15].

Alpha thioctic acid, a pathogenic treatment option, helps neutralize mitochondrial free radicals, increases glutathione concentration at the cellular level and, nevertheless, stimulates cellular antioxidants, for example vitamins C and E [11].

Thus, due to its anti-inflammatory and antioxidant effects, it contributes to improving the motor, autonomous and sensory symptoms in patients suffering from diabetic neuropathy [1,2,4].

Benfotiamine, which is a precursor of thiamine, represents a pathogenic treatment option, on one hand, it blocks alternative pathological pathways of hyperglycemia [2] and, on the other hand, it has antioxidant effects improving the speed of nerve conduction [14].

Gabapentin, pregabalin, duloxetine are included in the symptomatic treatment, which aims only to alleviate the painful symptoms and, consequently to improve the quality of life of the patients, without influencing the pathophysiological processes that lead to pain in diabetic neuropathy [14,15].

Along with these therapeutic options, other treatment strategies emphasize the importance of rigorous glycemic control, of reduced oxidative stress, which is associated with impaired autonomic nervous system and increased mortality [2,5] and, last but not least, the importance of treating risk factors, that include, on the one hand, dyslipidemia and, on the other hand, hypertension. Monotherapy, although considered a therapeutic option for patients with diabetic neuropathy, has often proved to be ineffective due to side effects of dose-dependent drugs [1].

Combined therapy represents an increasingly used treatment alternative today, as it is based, on the one hand, on the reciprocal potentiating effect of the drugs used and, on the other hand, the side effects of the drugs used have been cited much less frequently [15].

Conclusion

Finally, we demonstrated an increased response to combined therapy after one year of treatment that was also associated with short duration of diabetic neuropathy, insulin treatment, low glycated hemoglobin, absence of dyslipidemia or associated cardiovascular disease.

Thus, combined therapy is an alternative for reducing side effects and for increasing efficiency.

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