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COMPARISON OF EFFICACY OF NORTRIPTYLINE VERSUS TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION ON PAINFUL PERIPHERAL NEUROPATHY IN PATIENTS WITH DIABETES

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Abstract

Background and aims: *Diabetic peripheral neuropathic pain (DPNP) is one of the most common complications of diabetes and is difficult to treat. Existing treatments are often inadequate at controlling pain and limited by side-effects and drug tolerance. This study assessed the efficacy of nortriptyline versus Transcutaneous Electrical Nerve Stimulation (TENS) in patients with DPNP.* ***Material and method:*** *This is a randomized clinical trial study conducted on 39 patients with DPNP referring to Golestan Hospital in Ahvaz in 2017. Patients were randomly treated with TENS (18 sessions, each session 30 minutes; n=20) or nortriptyline (25 to 75 mg, once daily; n=19) for 6 weeks. Patients were evaluated for side effects and pain relief using visual analog scale (VAS).* ***Results:*** *There was a significant improvement in pain with both treatments compared with baseline ($p<0.001$). The patients in nortriptyline group experienced more pain relief (7.21±1.51 to 0.84±1.34) than the TENS group (7.6±1.47 to 2.75 ±2.43) (P=0.001). The 50% pain relief was observed in 14 patients (73%) in nortriptyline group, 6 patients (30%) in TENS group. Moreover, the side effects were seen in 15% of TENS and 55% of patients in nortriptyline groups (P=0.019).* ***Conclusion:*** *Both TENS and nortriptyline were effective and safe in the management of DPNP. But nortriptyline showed a better performance on pain relief.*

key words: *Transcutaneous Electrical Nerve Stimulation, Nortriptyline, Diabetic neuropathy, Diabetic peripheral neuropathic pain*

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Background and aims

Diabetic neuropathy is one of the most common and chronic microvascular complications of diabetes, which affects approximately 50% of people with diabetes [1]. Risk factors for peripheral neuropathy include poor glucose control, age, smoking and high blood pressure [2]. The pathological changes in the nerve-covering capillaries are associated with the severity of neuropathy. Ischemia, perivascular inflammation, persistent hyperglycemia, Nerve growth factor (NGF) and Nerve growth factor (NGF) have emerged as potential players in the pathogenesis of diabetic neuropathy [3-5].

Painful symptoms in peripheral neuropathy have been reported, such as burning sensation, feeling of getting needled, pulsating pain and excessive sensitivity. Approximately 10-20% of patients with diabetes have painful peripheral neuropathy [6,7].

Treatment for DPNP is based on a bilateral approach: modifying the underlying disease and controlling the symptoms of pain. Currently, the only treatment to eliminate the cause of DPNP is to control blood glucose. Also, a combination of drug and non-medicinal treatments should also be used to control the symptoms of DPNP [8,9].

Because of the uncertainty of the cause of diabetic peripheral neuropathy development, curative treatments using pain relievers, Tricyclic antidepressant (TCA) are the first line of DPNP treatment and are often the only way to alleviate the discomfort and pain in these patients [9]. The most important side effect of these drugs is anticholinergic effects. Therefore, although TCAs are low-cost and effective, some patients, especially the elderly, do not tolerate the anticholinergic and antihistamine effects, and are not usually recommended for people over the age of 50 years [10]. These medications can also cause dry mouth, weight gain, drowsiness, blurred vision, urinary retention, arrhythmias, and orthostatic hypotension [11]. On the other hand, the pain treatment criterion is negative in 75% of patients, which indicates the inadequacy of many of these pain relievers [12,13].

Since TCAs are now known to be similar in anti-pain properties. Therefore, among the drugs of this group, nortriptyline, which is less anticholinergic and easier to tolerate, should be considered for treatment [10].

Today non-medicinal strategies are of great importance because of the appearance of fewer side effects [14,15]. One of the non-medicinal treatments for pain is numerous forms of electrotherapy. In previous studies, the positive effect of electrical stimulations on the pain reduction in individuals with diabetic neuropathy has been more or less determined that among the various types of electrical stimulation performed for this group, the electrical stimulation of the nerve by the skin (TENS) has more evidences [16,17].

TENS is known as one of the non-medicinal treatments of chronic pains following neuropathy. In this method, the electric current is applied through the surface electrodes to the peripheral sensory nerves. These electrical stimuli, depending on the frequency used, can reduce pain and analgesia by stimulating the pain-transmitting nerves [2,18].

To the best of our knowledge, no direct head-to-head comparison has been conducted between TENS and nortriptyline for the treatment of DPNP. Therefore, this randomized clinical trial was performed to compare the safety and efficacy of TENS and nortriptyline on reduce pain in patients with DPNP to provide an appropriate strategy in terms of cost-benefit for the treatment of these patients.

Material and method

Study design

The present study is a randomized clinical trial that was conducted with the aim of comparing the effectiveness of nortriptyline and TENS on patients with peripheral neuropathic pain caused by type I and type II diabetes patients referring to diabetes clinic in Golestan, Ahwaz, Iran in 2017. After obtaining permission from the ethics committee of Jundishapur University of Medical Sciences, Ahwaz (code of ethics: IR.AJUMS.REC.1396, 605), all patients included in the study with awareness and by acquiring their written consent. This study was also registered in the Iran's clinical trial system (clinical trial code: IRCT20180212038705N2).

Patients

The sample size was calculated with 90% power test at a significance level of 5%, with a 95% confidence interval and considering VAS as the main variable in the study (19) a sample size of 21 patients was calculated in each group using the following formula:

$$N=\frac{\left(Z1-\alpha^2+Z_{1-\beta}\right)2\,(S_1^2+S_2^2)}{(X_1-X_2)2}$$

In this study, adult patients (over 18 years of age) with type 1 and type 2 diabetes were participated. Also, based on biography (burning pain, stinging, burning, which has started from the distal of lower extremity, in the form of a bilateral symmetry), physical examination, MNSI questionnaire (earning the minimum score of 3) and NCVs were diagnosed as diabetic neuropathy and had the minimum score of 4 for daily pain VAS based on VAS criteria were included in the study. All patients were also treated with pill, insulin or diet, and did not use any medication to treat or reduce the pain associated with neuropathy.

Patients with mood disorder, generalized anxiety disorder, heart disease, such as DHF, arrhythmias, recent cardiac ischemia, narcotic drug and alcohol abuse, liver disease, GFR <30ml /min, uncontrolled acute closed-angle glaucoma, epileptic seizures, lactating women, pregnant women, peripheral vascular disease, the presence of neuropathy due to other causes (renal failure, liver disease, hereditary or occupational neuropathies, immunity and alcohol consumption), receiving the drug for the control of DPNP during 2 weeks prior to the study, 12 <HbA1C and the history of diabetes of less than one year old were excluded from the study.

Randomization and Intervention

Before the beginning of treatment, the demographic information of each patient (age and gender) and clinical information including duration of diabetes, type of diabetes treatment and the results of blood glucose tests of patients were recorded. Then, the samples of the study were randomly divided into two groups A and B based on randomized quadrupole permutations. The first group was treated with nortriptyline with an initial dose of 25 mg daily for 6 weeks and ultimately increased to 75 mg per day based on patient tolerance and response to treatment.

The second group was also treated with TENS treatment for 6 weeks. In the TENS treatment method, the electrodes of the device were placed on the peroneal nerve pathway, with the anode on back of the external malleoli and the cathode on the head of the fibula. Electric stimulations with a frequency of 4 Hz were performed in the form of asymmetric pulses with a duration of 200 microseconds and with FM modulation on the patient's peroneal nerve pathway. The duration of each treatment session was 30 minutes and was performed for 3 days a week.

During the study, patients were asked to regularly take their medications on a regular basis and avoid taking other medications other than blood glucose control drugs and inform the researchers if any symptoms were observed

Follow up and Evaluation of Patients

Patients were examined on a weekly basis in terms of pain severity and side effects of medications (by internal resident). In cases where the patient did not have a referral for follow up, the follow up was done by making a phone call.

The analysis of pain changes based on visual analogue scale (VAS) was measured in patients at the beginning of the study and then every week. What is measured by the VAS scale is the score that the patient gives to his/her average 24-hour pain. This scale varies from 10 (maximum pain) to zero (analgesia state). Finally, the mean of pain intensity changes based on the number of VAS obtained was calculated and compared with each other in two groups.

Also, in nortriptyline group the side effects (dizziness, drowsiness, nausea, vomiting, weight gain, anorexia, dry mouth and insomnia) were evaluated on a weekly basis. The drug use compilation was examined by counting unused drugs by the patient at the end of each week. In TENS group dermatologic complications as the most important side effect of TENS evaluated weekly.

Statistical analysis

In the end, the collected data were analyzed by SPSS software version 20. In order to describe the quantitative data, the mean and standard deviation were used and for the qualitative variables frequency and percentage were utilized. Normality of the data was investigated by Kolmogorov-Smirnov test and homogeneity of variances was examined by Leven test. Also, for measuring the significance of differences and comparing the mean of quantitative and qualitative variables, independent t-test and Chi-square were used, respectively. Also, to compare the mean of variables at different times, Uni-variable analyses and repeated measurements analysis were used. The significance level in the tests was considered to be 0.05.

Results

Patients Disposition

In this study, among 280 patients with diabetes who referred to Golestan Gland Endocrinology Clinic, 42 patients were selected according to inclusion and exclusion criteria of the study and randomly assigned to two treatment groups. A total of 2 patients in the Nortriptyline group and 1 patient in the TENS group did not attend all follow-up visits due to either drug complications and change in treatment or inability to contact the patient; as a result, all the analyses were performed on 39 individuals. The diagram of the study process is shown in Figure 1.

Basic Characteristics of Patients

In the present study, 28 women and 11 men with an average age of 55.45 ± 7.93 participated (Table 1). There was no significant difference between the two groups in terms of age and gender ($p > 0.05$). Also, there was no significant difference between the two groups regarding the type of diabetes, the duration of diabetes, type of diabetes treatment and the results of laboratory parameters of blood glucose before the beginning of the study ($p > 0.05$) (Table 1).

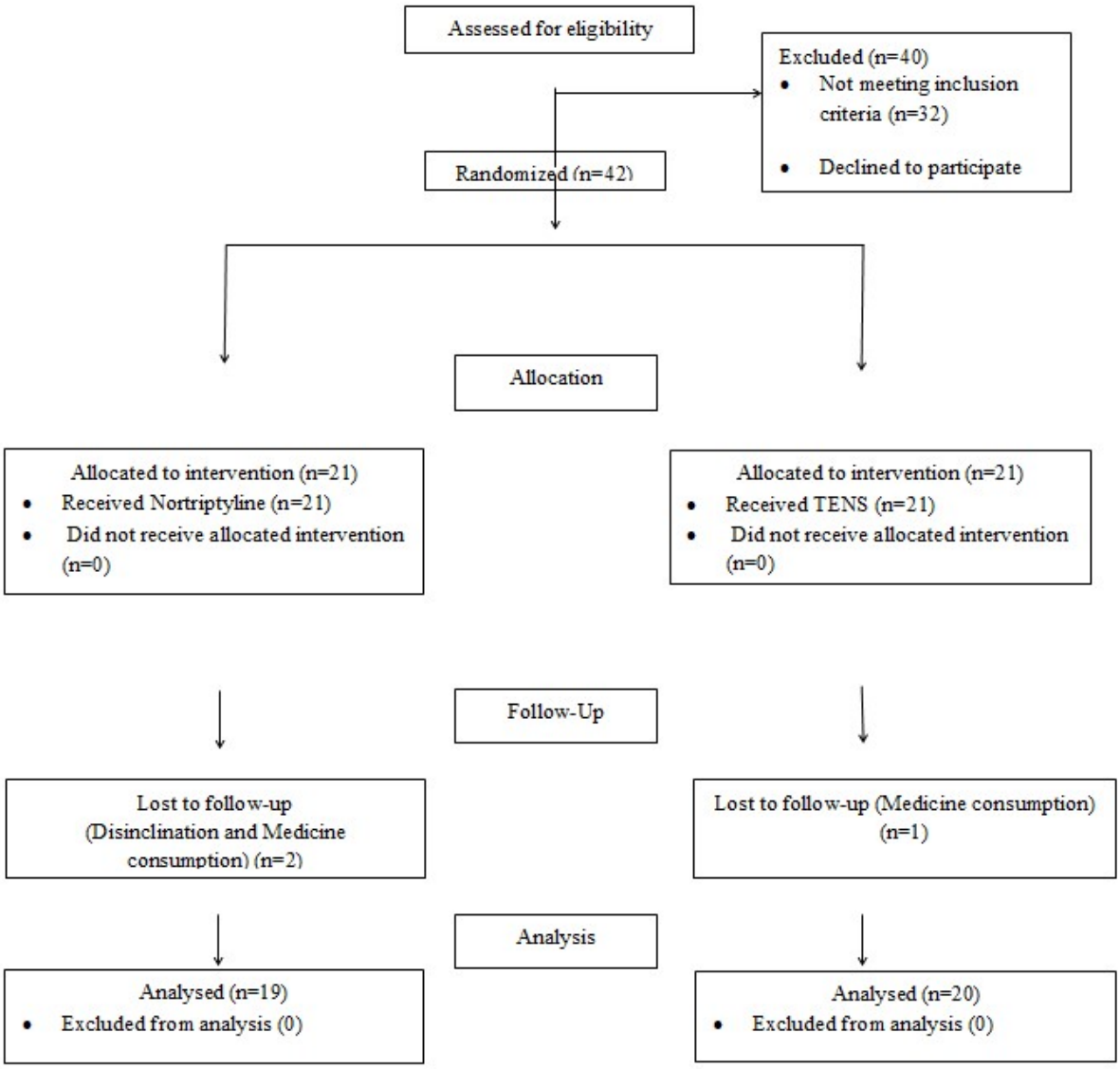

Figure 1. *Flow chart of the study.*

Table 1. Basic Characteristics of Patients in Two Groups.

Variable		Nortriptyline (n=19)	TENS (n=20)	P-value
Gender, n (%)	Male	6 (31.6)	5 (25)	0.648
	Female	13 (68.4)	15 (75)	
Age (Year)		55.5 ± 7.81	55.40 ± 8.05	0.971
Disease Duration (Year)		9.45 ± 4.75	9.58 ± 4.75	0.931
Diabetes Type	Type 1	4 (21.1)	1 (5)	0.182
	Type 2	15 (78.9)	19 (95)	
Diabetes Treatment Type	Insulin	10 (52.6)	9 (45)	0.624
	Pills	9 (47.4)	11 (55)	
HbA1c (%)		8.28 ± 0.59	8.23 ± 1.08	0.864
FBS (mg/dl)		197.42 ± 85.18	180.95 ± 54.57	0.474

TENS: Transcutaneous Electrical Nerve Stimulation; FBS: Fasting Blood Sugar

Effectiveness and Safety of Treatment

The results of the present study showed no significant differences in the pain intensity of patients based on the VAS criterion in two groups before the study (P = 0.419). But both groups had a significant decrease in pain amount during the treatment period (for each group, P <0.001) (Table 2 and Figure 2).

Table 2. *The Mean and Standard Deviation of Pain in Patients (VAS) in the Two Groups of the Study*

Follow-up Time	TENS (n=20)		Nortriptyline (n=19)		P-value
	Mean	Standard Deviation	Mean	Standard Deviation	
Pre-Treatment	7.6	1.47	7.21	1.51	0.419
1st Week	6.8	1.70	5.53	1.81	0.021
2nd Week	5.95	1.99	4.58	1.46	0.019
3rd Week	5.15	2.16	3.16	1.80	0.004
Fourth Week	4.15	2.35	1.84	1.61	0.001
Fifth Week	3.25	2.51	1	1.45	0.001
Sixth Week	2.75	2.43	0.84	1.34	0.001
P-value	< 0.001		< 0.001		-

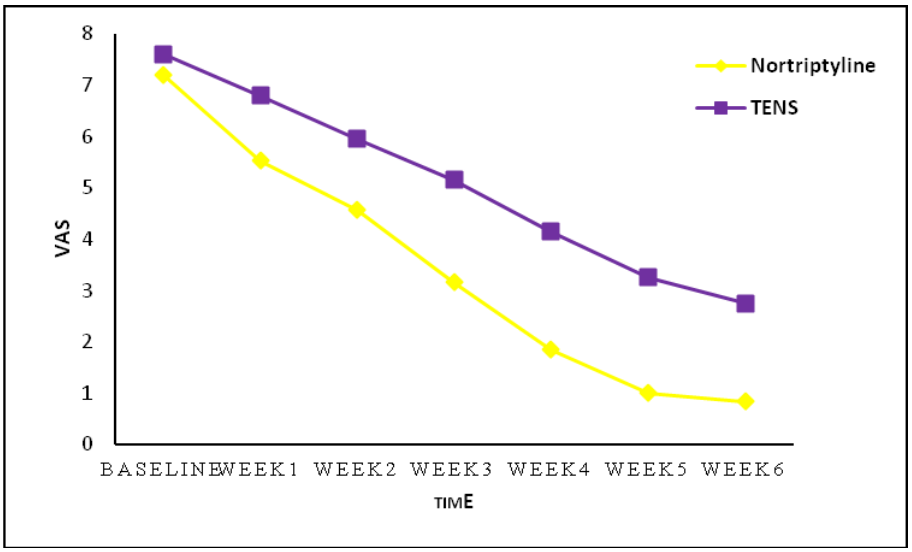

Figure 2. *Amount of Pain in Patients of Study Groups.*

The mean score of pain intensity in the nortriptyline group got from 7.17 ± 1.51 at the beginning of the study and reached to 0.84 ± 1.34 at the sixth week after treatment, and in the TENS group it got also from 7.6 ± 1.47 to 2.43 ± 75/2. Also, at all follow-up times after the beginning of treatment, patients of nortriptyline group experienced a greater reduction in pain than the TENS group, and the difference in pain amount between the two groups was statistically significant (P <0.05) (Table 2).

Also, the pain reduction of 50% was observed in 14 patients (73%) of the nortriptyline group and 6 patients (30%) in the TENS group, and there was a significant difference between the two groups in this respect

(P <0.0001). Results showed no statistically significant relationship between age, gender and duration of diabetes with pain extent in none of the two groups (P >0.05).

The results of Uni-variable analysis of pain in two groups at different times (regardless of other variables) showed that in the Nortriptyline group pain decreased with time (P <0.001). All times were significantly different two by two, but there were no significant differences between the 4th and the 5th weeks (P = 0/194) and the 5th week and the 6th week (P = 1/000), and the pain extent between weeks 1 and 2, there was also a boundary difference between the two groups (P = 0.092) and weeks 4 and 6 (P = 0.071). In the TENS group, the results also showed that there was a significant difference between the pain levels at all times of the study as two by two (P <0.001) (Figure 2).

The results of the study showed that in the first and second weeks after treatment, 11 patients (55%) of patients receiving Nortriptyline and 3 (15%) of patients receiving TENS, had side effects due to drug use, and there was a significant difference between the two groups (P = 0.019). These side effects are presented separately in Table 3. None of the patients report the side effects of the drug after the second week.

Table 3. Frequency of side effects of drug after treatment in two groups

	Drowsiness	Dry mouth	Vibration	Dizziness	Cramp	No	P-value
Nortriptyline	4 (21.1)	3 (15.8)	1 (5.3)	3 (15.8)	0	8 (42.1)	0.019
TENS	0	0	0	0	3 (15)	17 (85)	

The results of this study showed that the acceptance of treatment (compliance) in Nortriptyline group patients have been 90.47% and in TENS group it has been 95.23%. The dermatologic complications not observed in TENS group participants.

Discussion

Diabetic neuropathy is a heterogeneous and complex disorder characterized by a wide range of abnormalities; this abnormality effect of retinopathy is associated with progressively increasing risks of mortality [20]. In addition, diabetic neuropathy is a complication that affects about half of diabetic patients and their quality of life, leading to sleep disturbances and a patient's lifestyle [7].

Neuropathy pain is one of the most challenging pain syndromes, found in 8-26% of diabetic patients, but even using standard therapy methods, rarely, over 50% of patients are relieved and most patients suffer from pain. The goal of diabetic neuropathy treatment is to prevent the progression and to reduce the symptoms of disease [3].

The results of the present study in assessing the pain level of patients using Visual Analog Scale (VAS) showed that both Nortriptyline and TENS treatment methods significantly decreased the pain intensity in the subjects of the study, but the two groups showed a significant difference in pain level. These results also indicate that both drugs are effective in reducing pain in patients. However, pain reduction amount was higher in the nortriptyline group than that of the

TENS group, and this difference was statistically significant, and nortriptyline reduced the amount of pain more.

Hammack et al. (2002) conducted a randomized controlled trial for the effectiveness of nortriptyline in the treatment of paresthesia and neuropathy and its results showed that nortriptyline did not have a significant effect on paresthesia or pain in patients compared to placebo. These results are not consistent with the findings of the present study, because the present study showed that nortriptyline can significantly affect patient pain and can be used to reduce pain. This difference between the two studies can be attributed to the absence of the control group in the present study, as well as the difference in the society and the characteristics of the patients of the study [21].

On the other hand, Gilron et al. (2009) designed a study to investigate the effect of nortriptyline and gabapentin alone and in combination on painful diabetic neuropathy. In this study, the effect of drugs on pain relief of patients was evaluated and the results showed that 76% of patients in the nortriptyline group had more than 50% reduction in pain, which our study also confirms this finding [22]. In the present study, reduction of more than 50% of pain in 73% of patients in the Nortriptyline group was observed.

But in the study by Chandra et al. (2006), the reduction amount in pain intensity of patients treated with nortriptyline (25-50 mg per day for 4 weeks) was 47.22%, which is lower than that reported in the present study [23]. The reason for this difference in results can be related to the difference in the duration of the treatment, the characteristics of the patients and the method of assessing the severity of pain by the patients.

Various studies have been done on the effectiveness of TENS in treating patients with diabetic neuropathy. Forst et al. (2004) conducted a study to investigate the effect of TENS on diabetic neuropathy, the results of which showed the positive effect of this method on the pain of patients; which was also confirmed by the present study [24]. Yadav et al. (2013) also examined the effect of TENS on the reduction of neuropathic pain in 20 patients with diabetes, and the results showed that high-frequency TENS for 3 weeks could reduce neuropathic pains that the present study also confirmed this issue and showed that TENS can significantly reduce pain in patients [25]. In another study by Thakral et al., in 2013 it was also reported that electrical stimulations may be an alternative intervention in treating patients with diabetic peripheral neuropathy [26]. The effectiveness of TENS method (three consecutive hours per day for 3 weeks) was also reported in reducing the pain of patients with painful diabetic neuropathy in the study by Moharic et al. [27]. All of these results confirm the findings of the present study that the effectiveness of TENS in reducing the pain of DPNP patients.

On the other hand, Oyibo et al. (2004), in a study on patients with painful diabetic neuropathy, did not observe any evidence proving the efficacy of 6 weeks of electrical stimulation therapy in these patients [28]. These results are not consistent with the findings of the present study.

The reason for some differences in existing studies can be attributed to the difference in the population and sample size of the study, the difference in the pain measurement instrument, the different duration of the treatment, and also the error of self-reporting of the pain by the patient.

In the present study, the effectiveness of two therapeutic methods according to age, gender, duration of diabetes and type of diabetes treatment was also investigated that in this

regard, no difference was observed in the effectiveness of these two methods in either of these cases. Therefore, the above-mentioned variables do not affect the pain level of patients with DPNP.

In the present study, the extent of side effects of the study's two therapies was examined and it was determined that the level of side effects in the nortriptyline group is significantly higher than that of the TENS method (55% vs. 15%). In this study, the most side effects observed in Nortriptyline group was drowsiness. Also, in the TENS group, only 3 cases of muscle cramp were observed, which was not observed in any of the patients of the Nortriptyline group.

In the study by Chandra et al., 2006, also the amount of side effects resulting from nortriptyline consumption (mouth dryness, drowsiness, orthostatic hypotension) were observed in 58% of patients [23]. These results are consistent with the findings of this study. The complications resulting from consumption of nortriptyline in patients with diabetic neuropathy in the study by Khoromi et al., were 68.85%, and in the study by Gilron et al., it was also reported to be 68% [22,29]. These values are higher than the side effects observed in the present study, which is due to the higher dose of nortriptyline in these two studies (100 mg per day), as well as the difference in the studied population and the characteristics of the patients.

Finally, because there exist no similar studies conducted to directly compare the efficacy of TENS and nortriptyline, thus, it was not possible to compare the results of this study with other studies. But in general, the results of the present study showed that both of these therapy methods can be used as effective, inexpensive and safe medications for the treatment of patients with DPNP. But the effectiveness of Nortriptyline in reducing pain is better than TENS.

The Strengths and Weaknesses of the Study

Of the advantages and strengths of this study, the acceptance of the above treatment method (compliance) by the patients, which is one of the most important aspects of treatment and controlling disease, as well as the gradual increase of the consumed dosage of the drug, has resulted in better treatment outcomes.

On the other hand, the study also encountered some limitations, including the fact that the placebo group (placebo) was not taken into consideration in this study, which could show the sensitivity of the drugs used to reduce pain in patients with DPNP. Also, the duration of follow-up of patients was 6 weeks and therefore the long-term efficacy and safety of the medications were not investigated. It is suggested that in future studies, use newer drugs (such as duloxetine) as standard drug treatment.

Conslusion

The results of this study showed that both Nortriptyline and TENS methods have a positive effect on pain relief, but nortriptyline reduces more pain compared with TENS, so using nortriptyline is more suitable for patients needing severe pain relief. Also according to the results, although the extent of the complication in the Nortriptyline group has been high, but, due to the high degree of compliances of the patients in relation to this drug and the absence of any dangerous complications (such as arrhythmias), and due to the need for multiple referrals in the TENS group that make treatment process more difficult, Nortriptyline is recommended as the preferred treatment in DPNP.

But since the present study is the first direct clinical comparison in using TENS and nortriptyline in the treatment of DPNP, thus the

conclusion and decisive decision about the exact selection of the best treatment option require further studies with more sample sizes and for a longer duration.

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REFERENCES

1. Callaghan BC, Cheng HT, Stables CL et al. Diabetic neuropathy: clinical manifestations and current treatments. *Lancet Neurol* 11(6): 521-34, 2012.

2. Pieber K, Herceg M, Paternostro-Sluga T. Electrotherapy for the treatment of painful diabetic peripheral neuropathy: a review. *Journal of rehabilitation medicine* 42(4): 289-95, 2010.

3. Ziegler D. Painful diabetic neuropathy: treatment and future aspects. *Diabetes/Metabolism Research and Reviews* 24(1): 52-57, 2008.

4. Giacco F, Brownlee M. Oxidative stress and diabetic complications. *Circ Res* 107(9): 1058–1070, 2010.

5. Rübsam A, Parikh S, Fort P. Role of Inflammation in Diabetic Retinopathy. *Int J Mol Sci* 19(4): 942, 2018.

6. Klassen A, Di Iorio B, Guastaferro P et al. High-tone external muscle stimulation in end-stage renal disease: effects on symptomatic diabetic and uremic peripheral neuropathy. *J Ren Nutr* 18(1): 46-51, 2008.

7. Veves A, Backonja M, Malik RA. Painful, diabetic neuropathy: epidemiology, natural history, early diagnosis, and treatment options. *Pain Med* 9(6): 660-74, 2008.

8. Hovaguimian A, Gibbons, CH. Clinical approach to the treatment of painful diabetic neuropathy. *Therapeutic advances in endocrinology and metabolism* 2(1): 27-38, 2011.

9. Synder MJ, Gibbs LM, Lindsay TJ. Treating Painful Diabetic Peripheral Neuropathy: An Update. *Am Fam Physician* 1;94(3):227-34, 2016.

10. King, Steven A. Diabetic peripheral neuropathic pain: effective management. *Consultant* Oct. 2008, p. 825. Gale Academic Onefile, Accessed 5 Jan 2020.

11. Prescribing and Primary Care (PCA) team, Health and Social Care Information Centre. Prescription cost analysis, England 2013. *Health and Social Care Information Centre,* 2014.

12. Lindsay TJ, Rodgers BC, Savath V et al. Treating Diabetic Peripheral Neuropathic Pain. *American Family Physician* 82(2): 151-158, 2010.

13. Onge EL, Miller SA. Pain Associated with diabetic peripheral neuropathy. *Pharmacy and Therapeutics* 33(3): 166-176, 2008.

14. Alipour M, Malihi R, Hosseini SA et all. The effects of catechins on related risk factors with Type 2 diabetes: a review. *Progress in Nutrition* 20(1): 12-20, 2018.

15. Ashtary-Larky D, Ghanavati M, Lamuchi-Deli N et al. Rapid Weight Loss vs. Slow Weight Loss: Which is More Effective on Body Composition and Metabolic Risk Factors? *Int J Endocrinol Metab* 15(3): e13249, 2017.

16. Alberti KG, Zimmet P, Shaw J. International diabetes federation: a consensus on type 2 diabetes prevention. *Diabetic Medicine* 24(5): 451-463, 2007.

17. International Diabetes Federation. *IDF Diabetes Atlas. (6th ed).* Brussels, Belgium: International Diabetes Federation, 2013.

18. Cade WT. Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. *Physical therapy* 88(11): 1322-35, 2008.

19. Zakerkish M, Amiri F, Majdi Nasab N, Ghorbani A. Comparative Efficacy of Duloxetine Versus Nortriptyline in Patients with Diabetic Peripheral Neuropathic Pain: A Double Blind Randomized Controlled Trial. *Iran Red Crescent Med J* 19(8): e59995, 2017.

20. Cusick M, Meleth AD, Agrón E et al. Associations of mortality and diabetes complications in patients with type 1 and type 2 diabetes: early treatment diabetic retinopathy study report no. 27. *Diabetes Care* 28(3): 617-25, 2005.

21. Hammack JE, Michalak JC, Loprinzi CL et al. Phase III evaluation of nortriptyline for alleviation of symptoms of cis-platinum-induced peripheral neuropathy. *Pain* 98(1-2): 195-203, 2002.

22. Gilron I1, Bailey JM, Tu D, Holden RR, Jackson AC, Houlden RL. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial. *Lancet* 374(9697): 1252-61, 2009.

23. Chandra K, Shafiq N, Pandhi P et al. Gabapentin versus nortriptyline in post-herpetic neuralgia patients: a randomized, double-blind clinical trial—the GONIP Trial. *International journal of Clinical Pharmacology and Therapeutics* 44(8): 358-63, 2006.

24. Forst T, Nguyen M, Forst S et al. Impact of low frequency transcutaneous electrical nerve stimulation on symptomatic diabetic neuropathy using the new Salutaris device. *Diabetes, nutrition & metabolism* 17(3): 163-8, 2004.

25. Yadav AO, Ramteke G. Effectiveness of transcutaneous electrical nerve stimulator (TENS) in reducing neuropathic pain in patients with diabetic neuropathy. *Indian Journal of Physiotherapy and Occupational Therapy* 7(1): 11, 2013.

26. Thakral G, Kim PJ, LaFontaine J, Menzies R, Najafi B, Lavery LA. Electrical stimulation as an adjunctive treatment of painful and sensory diabetic neuropathy. *SAGE Publications Sage CA: Los Angeles, CA, 2013*.

27. Moharic M, Burger H. Effect of transcutaneous electrical nerve stimulation on sensation thresholds in patients with painful diabetic neuropathy: an observational study. *International Journal of Rehabilitation Research* 33(3): 211-7, 2010.

28. Oyibo S, Breislin K, Boulton A. Electrical stimulation therapy through stocking electrodes for painful diabetic neuropathy: a double blind, controlled crossover study. *Diabetic Medicine* 21(8): 940-4, 2004.

29. Khoromi S1, Cui L, Nackers L, Max MB. Morphine, nortriptyline and their combination vs. placebo in patients with chronic lumbar root pain. *Pain* 130(1-2): 66-75, 2007.