The Comparison of Effectiveness of TENS and Placebo TENS in Peripheral Neuropathic Pain in Patients with Type II Diabetes Mellitus

Tip 2 Diabetes Mellituslu Hastalarda Periferik Nöropatik Ağrıda TENS ve Plasebo TENS'in Etkinliğinin Karşılaştırılması

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ABSTRACT Objective: Diabetic peripheral neuropathic pain affects the functionality, mood, and sleep patterns of approximately 10 to 20 percent of patients with diabetes mellitus. Treatment goals include restoring function and improving pain control. In this study we aimed to compare the efficacy of transcutaneous electrical nerve stimulation (TENS) and placebo TENS in the treatment of peripheral neuropathic pain in patients with type II diabetes mellitus (DM). **Material and Methods:** Forty patients who were diagnosed as type II DM with peripheral neuropathy were enrolled to this study. Patients were randomly divided into two groups as Group A (n= 20) TENS group and Group B (n= 20) placebo TENS group. Forty-eight hours before the beginning of TENS therapy, the drugs used for the treatment of neuropathic pain were discontinued. The electrodes of the TENS were bilaterally placed on the lumbosacral region, 3 cm lateral of the vertebral column. The frequency of the electrostimulation which was used in Group A patients was 80 hertz and the amplitude was high enough to create paresthesia. No electrostimulation was given to Group B patients. TENS was applied 30 minutes daily and the procedure was continued for 20 days in both groups. Visual analog scale (VAS) scores and pain grades of the patients at certain times were taken into account for evaluating the effectiveness of the procedure. **Results:** The demographic data of the groups were not significantly different. Although VAS scores before procedure and on the 5th day of the procedure were not significantly different between groups ($p> 0.05$), VAS scores on 10th and 20th days of the procedure in Group A were significantly lower than Group B ($p< 0.001$). There was no significant difference between pain grades of Group A and B at the beginning of the study, but pain grades in Group A were significantly lower than Group B when evaluated at the end of the study ($p< 0.001$). **Conclusion:** Treatment of the patients with DN is a challenging for the physicians. TENS can be used as an efficient and safe treatment option especially in DN patients in whom pharmachologic treatment is contraindicated or inefficient. Placebo TENS has a limited placebo effect in diabetic neuropathy patients.

Key Words: Diabetes mellitus; diabetic neuropathies; transcutaneous electric nerve stimulation

ÖZET Amaç: Diabetik periferik nöropatik ağrı, DM'lu hastaların yaklaşık %10-20'sinde günlük aktiviteleri, duygu durumu ve uyku düzenini etkilemektedir. Tedavi amaçları fonksiyonları düzeltmek ve ağrı kontrolünü sağlamayı içerir. Bu çalışmada diabetes mellituslu hastalarda periferal nöropatik ağrı tedavisinde transkütanöz elektriksel sinir stimülasyonu (TENS) ve plasebo TENS'in etkinliğini karşılaştırmayı amaçladık. **Gereç ve Yöntemler:** Tip 2 diabetes mellitus tanısı almış periferik nöropatili kırk hasta çalışmaya dahil edildi. Hastalar iki gruba randomize edilerek TENS alanlar Grup A (N= 20), plasebo TENS alanlar Grup B (N= 20) olarak ayrıldılar. Periferik nöropati için kullanılmakta olan ilaçlar TENS tedavisinden 48 saat önce kesildi. TENS için elektrodlar lumbosakral bölgede vertebral kolonun 3 cm lateraline yerleştirildi. Grup A'daki olgularda elektrostimulasyon frekansı 80 Hz ve amplitüd parestezi oluşturacak ölçüde yüksek tutuldu. Grup B olgularına hiç elektrostimülasyon verilmedi. Her iki grupta TENS günde 30 dk olarak 20 gün uygulandı. İşlem etkinliğini belirleyebilmek amacıyla hastalarda belli zaman aralıklarıyla vizüel analog ölçeği (VAS) skorları ve ağrı dereceleri ölçüldü. **Bulgular:** Gruplar arasında demografik veriler yönünden anlamlı farklılık yoktu. İşlem öncesi ve işlemin 5. gününde VAS skorları yönünden gruplar arasında farklılık olmamakla birlikte, Grup A'nın 10. ve 20. günlerdeki VAS skorları grup B'ninkilerden anlamlı olarak daha düşüktü. Çalışma başlangıcında gruplar arasında ağrı dereceleri yönünden fark olmamasına rağmen, çalışma sonunda Grup A'nın ağrı dereceleri Grup B'ninkilerden anlamlı derecede daha düşüktü. **Sonuç:** Diabetik nöropatik ağrısı olan hastaların tedavisi ciddi bir problemdir. TENS özellikle farmakolojik tedavinin kontrendike veya yetersiz olduğu diabetik nöropati hastalarında etkin ve güvenilir bir tedavi seçeneğidir. Plasebo TENS diabetik nöropatik ağrıda sadece sınırlı plasebo etki göstermiştir.

Anahtar Kelimeler: Diabetes mellitus; diyabetik nöropatiler; transkütanöz elektriksel sinir stimulasyonu

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Diabetic neuropathy (DN), which is the most frequently seen type of neuropathy, is a common complication of diabetes mellitus (DM) that is often associated with considerable morbidity and mortality.[1] DN affects 20-30% of diabetic patients.[2] In several studies, plasma glucose levels were found as the most important determining factor for DN and it is shown that the occurrence of DN was related to age, male sex, height and duration of the DM.[3] Patogenesis of diabetic neuropathy is complex. Chronic hyperglycemia is a major factor that induces nerve fiber injury. High level of glucose stimulates the polyol pathway causing osmotic stress and enhance reactive oxygen species generation.[4] Increase in reactive oxygen products and proteinkinase C pathway activation causes endoneural microvascular changes which leads to ischemia and hypoxia.[5] Recent studies concerning the vascular hypothesis, oxidative stress, the neurotrophic hypothesis, as well as the possibility of the role of autoimmunity have revealed new therapeutic options for DN.[1]

Treatment of the patients with DN is challenging for the physicians. The aim of the treatment is to correct the mechanism that causes neuropathy and to improve the symptoms. The treatment of neuropathic pain is largely empirical, often relying on data from clinical trials and case reports. However, it is necessary to achieve a strict glisemic control and to treat pain by using analgesic agents, but these agents are usually insufficient in this type of pain.[6] Consequently, diverse treatments are used, including non-invasive drug therapies (antidepressants, antiepileptic drugs and membrane stabilizing drugs), invasive therapies (nerve blocks, ablative surgery), and alternative therapies (e.g., acupuncture, TENS).[7]

Transcutaneous electrical nerve stimulation (TENS) is a procedure in which nervous system is stimulated by using controlled, low voltage electrical stimulations. TENS is used widely because it is efficient, easily used and has few side effects.[8] Two different theories have been proposed for the mechanism of action of TENS. The most popular theory is the gate control theory of pain. This theory proposes that stimulation of large-diameter afferent fibers inhibits second-order neurons in the dorsal horn and prevents pain impulses carried by small-diameter fibers from reaching higher brain centers. The second explanation for the mechanism of action of TENS is that it stimulates the release of endogenous opioids. Naloxone, an opioid receptor antagonist, blocks the analgesia produced by low-frequency electroacupuncture.[9]

In this study, we aimed to evaluate the effectiveness of TENS in pain caused by diabetic neuropathy and compare the efficacy of TENS with placebo TENS.

MATERIAL AND METHODS

Forty ASA I-III patients who were diagnosed with type II DM and peripheral neuropathy who had the symptoms and signs of peripheral neuropathy in lower extremities at least in previous 6 months were enrolled to this study after the permission of local ethics committee and written informed consents of the patients. The patients have used different medical treatment options like gabapentin, pregabalin, amitriptyline, tramadol and even non-steroidal anti-inflammatory drugs several times during their illness, but they still had neuropathic pain complaints. Exclusion criteria were pregnancy, patients with electrical stimulation device, clinically apparent vascular insufficiency in extremities, claudicatio intermittens, cerebrovascular ischemia, psychiatric disease, dementia and irritation or ulceration in skin.

Blood glucose levels of the patients were measured four times a day during the study and the values were below 200 mg/dl. Patients with uncontrolled glucose levels were not included in the study.

In order to determine 50% decrease in VAS values, sample size of each group should be 19 while Type I error α= 0.05 and Type II error β= 0.01.

Patients were randomly divided into two groups as Group A (n= 20) TENS group, and Group B (n= 20) placebo TENS group. Forty-eight hours before the beginning of TENS therapy, the drugs used for the treatment of neuropathic pain (analgesics, tricyclic antidepressants etc.) were discontinued. According to the table used for grading pain, the

patients graded their pain as 2,3,4,5 were enrolled to the study. The procedure, TENS device and Visual Analog Scale (VAS) were explained to the patients before the therapy. Double channel TENS device (Aukewel, AK-2000-III, Health Messenger) with four electrodes was used. After skin cleaning and applying hydrophilic gel to the electrodes, the electrodes were bilaterally applied 3 cm lateral to the vertebral column on the lumbosacral region.

Electrostimulation with a frequency of 80 Hertz and an amplitude high enough to create paresthesia was used 30 minutes daily for 20 days in Group A. The amplitude was increased gradually to the peak point that neither disturbed the patient nor created muscle contraction. Before each sequence this amplitude level was established for each patient.

In Group B, the electrodes were applied to the same region of patients and electrostimulation with a low amplitude was given to the patients and then TENS device was switched off.

Patients in Group B were informed that they might not be feeling the stimulation but it was not necessary. This procedure was performed 30 minutes daily for 20 days. Active TENS was planned for this group after our study finished. Age, gender, neurological symptoms of the patients and duration of DM were recorded.

VAS scores were recorded before and 5th, 10th and 20th days of the procedure. Pain grades of patients were recorded before study and on 20th day of the procedure. Side effects due to TENS application were also recorded. Criteria used for grading pain were the following:[10]

Grade 0: No symptoms.

Grade 1: Minimal burning pain with or without paresthesias. Some discomfort but bearable. Insignificant problem in daily activities.

Grade 2: Mild burning pain with or without paresthesias. Uncomfortable most of the day. Occasional pain during night. Some disturbance of daily activities. Patient wants treatment.

Grade 3: Burning pain of moderate intensity with paresthesias disturbing the night sleep. Distressing and distracting causing difficulty in daily activities.

Grade 4: Intense burning pain, intermittent. Presence of parasthesias. Significantly disturbed night sleep due to pain. Unbearable. Patient unable to function.

Grade 5: Extremely intense burning pain, constant, excruciating. Presence of paresthesias. Very disturbed night sleep. Patient asking for strong analgesics.

Statistical analyses were performed using Mann Whitney U test and student's t test.

RESULTS

No statistically significant difference was found between demographic charecteristics of the groups ($p > 0.05$) (Table 1).

When side effects were compared, there was no difference between the groups, except skin irritation only in one patient in Group A ($p > 0.05$).

Although VAS scores before procedure and on 5th day of the procedure were not significantly different between groups ($p > 0.05$), VAS scores on 10th and 20th days of the procedure in Group A were significantly lower than Group B ($p < 0.001$) (Figure 1).

There was no significant difference between pain grades of Group A and B at the beginning of the study, but pain grades in Group A were significantly lower than Group B at the end of the study ($p < 0.001$) (Figure 2).

DISCUSSION

TENS is widely used in treatment of chronic pain. It has also been used in DN as an alternative treatment.[11-13]

TABLE 1: Demographic characteristics of the patients.

	Group A (n= 20)	Group B (n= 20)	p
Age (year)	58.45 ± 15.9	62.05 ± 19.9	0.531
Gender (Female/Male)	12/8	11/9	0.990
Duration of DM (year)	11.85±1.48	11.45±0.91	0.309
Duration of DN (year)	3.95±0.55	3.60±0.56	0.053

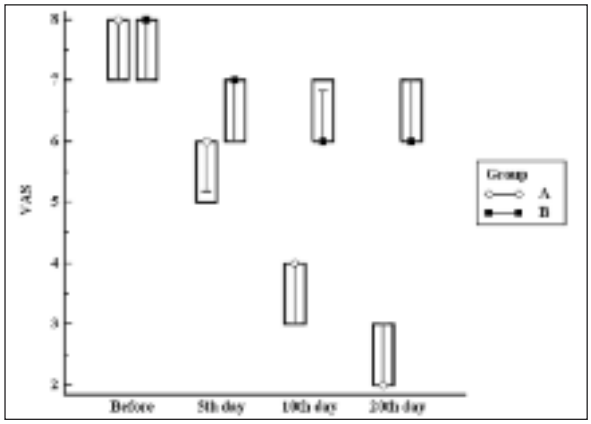

FIGURE 1: VAS scores of the groups before and during the treatment.
Median (95%CI).
VAS: Visual analog scale.

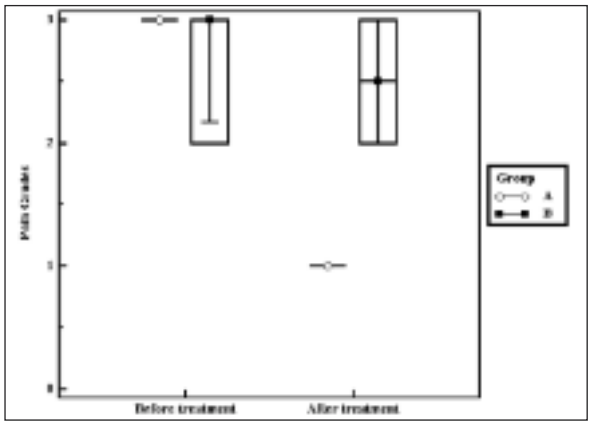

FIGURE 2: Pain grades of the groups before and after the treatment.
Median (95%CI).
VAS: Visual analog scale.

We assessed the efficacy of TENS and placebo TENS in DN. There was a significant difference in VAS scores on the 10th and 20th days of the treatment and pain grades after the treatment between Group A and Group B. There was a slight decrease in VAS scores and pain grades after treatment in placebo group, but the decrease was not significant. Psychologic factors also play a role in chronic pain. However, in our study, it was not clear whether psychologic factors had a role in this limited placebo effect formed by TENS.

Placebo effect of TENS was assessed in a number of studies. In a study, Thornsteinson applied active TENS for 20 minutes on three consecutive days and placebo TENS on following three days to 93 patients with chronic pain. They used two different TENS devices for active and placebo application. At the end of the study, patients were asked to choose one of the devices and most of the patients chose the active electrotherapy applying device.[14]

In a study, Marchand et al. randomized 42 patients with low back pain into three groups as electrotherapy group, placebo group and control group. TENS was applied two times a week for 30 minutes for a 10 week period. Pain in active electrotherapy group decreased when compared to placebo group after one week. However, there was no difference between pain scores of the groups during 3-6 months follow-up period. It was concluded that the effect of TENS lasted short and TENS should be applied in a multidisciplinary approach combined with other pharmacologic agents.[13]

TENS is a frequently applied therapy in chronic pain although evidence for effectiveness is inconclusive. Several types of TENS exist, based on different combinations of frequency, pulse duration and intensity. The precise mechanism of action and the relevance of combinations of stimulus parameters are still unclear. Köke et al. compared the effectiveness of TENS adjusted to different levels of frequency and intensity in 180 chronic pain patients who were randomized into three groups. No differences were found in patients' assessment. They made no definite conclusions on effectiveness of TENS in the treatment of chronic pain.[11]

Kumar and Marshall applied active and placebo TENS to patients with DN. They observed minimal placebo effect, but symptoms improved better in active TENS group. Then, active TENS was applied to patients in placebo group and symptoms were improved significantly after active TENS therapy.[10]

In a study by Gieue et al., the analgesic effects of TENS and vibratory stimulation, used both separately and simultaneously, were compared in 24 patients suffering from chronic pain They observed that dual stimulation had stronger and more long-lasting analgesic effects.[15]

The efficacy of TENS is also associated with the underlying pathology. Meyler et al. have used

TENS in 193 chronic pain patients for six months and they observed satisfactory improvement in 53% of pain caused by peripheral nerve damage, 69% of musculoskeletal pain and 75% of anginal pain resulting from ischemic heart disease. There was no response to the treatment in patients with psychologic and social problems.[12]

Johanson et al. applied high frequency TENS during three different times (120, 60, 30 minutes) to 72 patients with chronic pain. They observed 50% reduction in pain scores of patients. Improvement in pain scores was usually seen between the 3rd and 6th days of therapy. The best scores were seen in patients in whom TENS was applied for 120 minutes (50-100%) and improvement in pain was minimal in patients in whom TENS was applied for 30 minutes or less (20%). Patients with neurogenic pain, pain on extremities, low CSF endorphine levels and in whom electrodes placed on pathways of main nerve trunks responded better to TENS therapy.[16]

In a double blind, randomized study, Forst et al. compared 19 patients suffering from mild-to-moderate symptomatic DN who received either treatment with TENS or a placebo TENS. They concluded that TENS was a convenient, non-pharmacological option for primary or adjuvant treatment of painful diabetic neuropathy.[17]

Our study group included patients only with DN. Pain was localized to feet, leg and/or thigh. We observed 75% and 10% reduction in pain grades of patients in active electrotherapy and placebo groups, respectively. Decrease in pain grades started approximately on the 10th day of therapy in patients receiving active electrotherapy. VAS scores on the 10th and 20th days of therapy were significantly lower than basal VAS scores.

Electrodes can be placed on different areas on body during TENS therapy in chronic pain patients. It is reported that electrodes can be placed on the painful area, proximal or distal to painful area or on the area that the nerve, which innervates the painful area, travels nearest to the surface of the body.[18]

The effect of placement of the electrodes in TENS therapy was discussed in a number of studies. Rao et al. placed the electrodes to three different areas during TENS therapy in 114 chronic pain patients. Electrodes were placed to the painful area, proximal to the peripheral nerve which innervated the painful area or paravertebral area of associated nerve root. TENS therapy was effective after 1-5 treatment sequences. They observed no relationship between electrode placement and improvement of pain. They concluded that TENS was effective especially in patients with peripheral neuropathy and received no other treatment regimen before.[19]

Somers and Somers applied TENS to a patient with pain in left lower limb because of diabetic neuropathy. The pain did not respond to oral analgesic agents, benzodiazepines and tricyclic antidepressant therapy before. They placed the electrodes to lumbar paravertebral region and they observed 38% decrease in pain after the first TENS therapy.[20]

Mannheimer and Carlsson compared two different stimulus frequency and electrode placement in 19 patients with rheumatoid arthritis. They showed that high stimulus frequency and electrodes placed on painful area were more effective than low stimulus frequency and electrodes placed distally.[21]

In our study, we placed the electrodes to lumbosacral paravertebral region in patients with DN in lower limbs.

Skin may not be intact and pain perception can be disturbed in patients with diabetic neuropathy in lower limb. Pain perception of back is rarely disturbed, and dorsal rami of sacral and lumbar nerves innervate this area. Therefore, we placed the electrodes to the lumbosacral paravertebral region.[20]

Agents used for the pharmachologic treatment of DN can cause various side effects, like pancytopenia, dry mouth, sedation, nausea-vomiting, hepatitis, gastritis, nephrotoxicity, abormal ECG and hypoglycemia.[11,22] Application of TENS may be an effective treatment for the pain of diabetic neuropathy especially in patients pharmachologic treatment is contraindicated.

In our study we observed skin reaction related to electrode in only one of 40 patients.

TENS is an alternative therapy which is successfully used in DN without any side effects.

TENS is a safe method that can be used in treatment of pain also in elderly. It has an important role in treatment of especially DN, rehabilitation after fractures and anginal pains.[14,23]

Efficacy of TENS increases with high frequency, long time and frequent application. If indications, etiology of pain and psychologic state of patients are evaluated well, TENS can be an alternative and an adjunctive method in treatment of chronic pain.

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