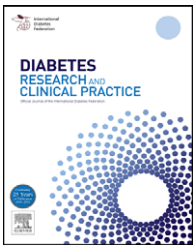
Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation



Effect of transcutaneous electrical nerve stimulation on symptomatic diabetic peripheral neuropathy: A meta-analysis of randomized controlled trials

Dong-mei Jin [a], *Yun Xu* [b], *Deng-feng Geng* [c,*], *Tie-bin Yan* [a]

[a] *Department of Rehabilitation Medicine, Sun Yat-sen Memorial Hospital, Zhongshan University, Guangzhou 510120, PR China*
[b] *Department of Endocrinology, The First Affiliated Hospital, Zhongshan University, Guangzhou 510080, PR China*
[c] *Department of Cardiology, Sun Yat-sen Memorial Hospital, Zhongshan University, No.107 Yanjiang Road, Guangzhou 510120, PR China*

ARTICLE INFO

Article history:
Received 20 January 2010
Received in revised form
17 March 2010
Accepted 29 March 2010
Published on line 26 May 2010

Keywords:
Diabetic neuropathies
Transcutaneous electric nerve stimulation
Pain
Randomized controlled trial
Meta-analysis

ABSTRACT

Aims: To evaluate the effectiveness of transcutaneous electrical nerve stimulation (TENS) on diabetic peripheral neuropathy (DPN).
Methods: Randomized controlled trials (RCTs) comparing TENS with routine care, pharmacological interventions or placebo devices on patients with symptomatic DPN, were identified by electronic and manual searches. Studies were selected and available data were extracted independently by two investigators. Meta-analysis was performed by RevMan 4.2.8 software.
Results: Three RCTs involving 78 patients were included in this study. The reductions in mean pain score were significantly greater in TENS group than in placebo TENS group in 4 weeks and 6 weeks follow-up [4 weeks, SMD-5.37, 95% CI (−6.97, −3.77); 6 weeks, SMD-1.01, 95% CI (−2.01, −0.01)], but not in 12 weeks follow-up [SMD-1.65, 95% CI (−4.02, 0.73)]. TENS therapy was associated with significantly subjective improvement in overall neuropathic symptoms in 12 weeks follow-up [WMD-0.18, 95% CI (−0.32, −0.051)]. No TENS-related adverse events were registered in TENS group.
Conclusions: TENS therapy may be an effective and safe strategy in treatment of symptomatic DPN. Due to small sample and short-term treatment duration, large multi-centre RCTs are needed to further evaluate the long-term effect of TENS on DPN.

1. Introduction

Diabetic peripheral neuropathy (DPN), which is a common complication of diabetes, accounts for 12.3% at original diagnosis of diabetes and 30–50% after 12 years history of diabetes [1,2]. Up to 20% of patients with DPN have symptoms such as chronic pain, hyperalgesia or numbness in the distal limbs [3], which severely impair their life quality. Furthermore, DPN is an independent risk factor for diabetic foot which is responsible for 50–75% of non-traumatic amputations [4]. It is reported that the annual cost of DPN together with its complications in the US varies between 4.6 billion and 13.7 billion dollars accounting for 27% of the direct medical cost of diabetes [5].

Tricyclic antidepressants, currently the first-line agent for the treatment of painful DPN, are effective in only 50% of

* *Corresponding author*. Tel.: +86 20 81332361; fax: +86 20 81332623.
E-mail address: dfengg@hotmail.com (D.-f. Geng).
0168-8227/$ – see front matter
doi:10.1016/j.diabres.2010.03.021

patients, while on the hand imposing adverse effects on 60–80% of patients, resulting in some patients to withdraw from treatment [6].

Transcutaneous electrical nerve stimulation (TENS) is a therapy in which units stimulate peripheral nerves via skin surface electrodes, which are placed on the lower extremities according to the distribution of nerve fibres, at well tolerated intensities and are capable of being self-administered. Recently small sample clinical trials have evaluated the effect of TENS on painful DPN, however, the results were inconsistent across trials. In this study, we performed a meta-analysis of all relevant randomized controlled trials (RCTs) to evaluate the effect of TNES therapy on symptomatic DPN.

2. Method

2.1. Search strategy

Electronic databases including PubMed, EMBase, Cochrane central register of controlled trials (2nd Quarter 2009), CINAHL, BIOSIS Previews, physical therapy, pain research at oxford, the Journal of the American Physical Therapy Association web sites and Chinese Biomedical Database were searched in the 1980–2009 time period by using the Mesh and text keywords: *random*; *diabetic peripheral neuropathy*; *pain and transcutaneous electric nerve stimulation*. References from these trials were scrutinized to reveal additional citations. In addition; Conference Proceedings from American Diabetes Association; the European Association for the Study of Diabetes; and the supplements of American Journal of Physical Medicine and Rehabilitation; Archives of Physical Medicine and Rehabilitation; Clinical Rehabilitation; Pain were also searched. There were no limitations in languages and publications.

2.2. Criteria for study selection

Studies considered for inclusion met the following criteria: (i) type of study design was RCTs; (ii) type of participants were patients with symptomatic DPN; (iii) type of intervention was TENS therapy compared with routine care, pharmacological interventions or placebo devices; (iv) type of outcome measures included pain relief, overall neuropathic symptoms and adverse effects. RCTs concerned with invasive approaches such as electrical spinal-cord stimulation and acupuncture were excluded. All types of TENS machines were included in this study.

2.3. Outcome measures

The primary outcome measure was pain relief. The secondary outcome measures of interest were subjective improvements in overall neuropathic symptoms, including hyperalgesia, numbness and quality of life. The adverse effects were also analyzed.

2.4. Data extraction

Data were extracted independently by 2 investigators. Discrepancies were resolved by consensus or a third author adjudication. The following data were extracted from each included study: data regarding patient demographics, information about study design (methods of random, blind, allocation concealment and follow-up), interventions in each group and outcome measures of interest.

2.5. Statistical analysis

We referred to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions 4.2.5 [7] in this meta-analysis. Results were expressed as relative risk (RR) with 95% confidence intervals (CIs) for dichotomous outcomes. As for continuous outcomes, if unit of measurement was consistent across trials, results were presented as weighted mean difference (WMD) with 95% CIs, and if inconsistent, results were expressed as standard mean difference (SMD) with 95% CIs. Heterogeneity across trials was assessed via a standard Chi square test with significance being set at $P < 0.10$ and also assessed by means of I^2 statistic with significance being set at $I^2 > 50\%$. Random effects model was used for statistical analysis due to wide clinical and methodological variability across the trials. Statistical analysis was performed using Review Manager 4.2.8 (The Cochrane Collaboration, Oxford, England). A value of $P < 0.05$ was considered statistically significant.

3. Results

3.1. Study selection

Three trials [8–10] with 78 patients were identified for inclusion from 130 potentially relevant publications. Five other RCTs [11–15] were excluded: one RCT [11] compared TENS therapy with high frequency external muscle stimulation; outcome measures in one RCT [12] did not meet with the inclusion criteria; the other three RCTs [13–15] applied invasive treatment such as electrical spinal-cord stimulation and percutaneous electrical nerve stimulation.

3.2. Baseline characteristics and study quality

Table 1 summarizes baseline characteristics and the assessment of study quality in accordance with CONSORT statement [16]. The confounding factors were well balanced in each arm. Male patients accounted for 43.8%.

3.3. Mean pain score reduction

Three RCTs [8–10] compared the effectiveness of TENS therapy on mean pain score reduction in patients with symptomatic DPN with inactive stimulation. The reductions in mean pain score were significantly greater in TENS group than in placebo TENS group in 4 weeks and 6 weeks follow-up [4 weeks, SMD-5.37, 95% CI (−6.97, −3.77); 6 weeks, SMD-1.01, 95% CI (−2.01, −0.01)], but not in 12 weeks follow-up [SMD-1.65, 95% CI (−4.02, 0.73)] (Fig. 1).

Kumar et al.'s study [9] showed that TENS therapy was effective in relief of pain in patients who failed to respond to amitriptyline. Besides, TENS in combination with amitriptyline

Table 1 – Baseline characteristics and study quality.

Study	Kumar [8]	Kumar [9]	Forst [10]
No. of patients, *n*			
Total	31	23	24
TENS group	18	14	13
Placebo TENS group	13	9	11
Age (years)			
TENS group	53 ± 4	59 ± 2	57.6 ± 11.5
Placebo TENS group	59 ± 3	58 ± 4	59.4 ± 8.6
Sex(F/M), *n*			
TENS group	11/7	10/4	6/6
Placebo TENS group	8/5	3/6	3/4
Duration of DM (years)			
TENS group	9 ± 2	8 ± 1	15.9 ± 8.3
Placebo TENS group	12 ± 2	7 ± 2	18.4 ± 11.0
Duration of DPN (months)			
TENS group	16 ± 3	22 ± 6	–
Placebo TENS group	22 ± 4	21 ± 5	–
BMI (kg/m^2)	–	–	–
TENS group	29.2 ± 2.9	32.4 ± 1.8	–
Placebo TENS group	30.5 ± 9.8	32.4 ± 2.9	–
Intervention			
TENS group	TENS: 30 min d^{-1} × 4 w (pulse width 4 ms, ≥2 Hz)	0–4 w:amitriptylin 4–16 w: TENS + amitriptylin 16–20 w:amitriptylin (TENS: pulse width 4 ms, 2–70 Hz;)	TENS:30 min d^{-1} × 12 w(4 Hz/280 μs; 5–70 mA)
Placebo TENS group	Placebo	Placebo	Placebo
Outcome measures	1. Pain score[a] 2. Subjective improvement in overall neuropathic symptoms[a]	1. Pain score[a] 2. Subjective improvement in overall neuropathic symptoms[a]	1.Pain score[b] 2. Subjective improvement in overall neuropathic symptoms[b] 3. Sensory nerve threshold
Study quality			
Reporting of randomization	Y	Y	Y
Generation of random sequence	Unclear	Unclear	Computer generated randomization list
Allocation concealment	Unclear	Unclear	Unclear
Blinding	Patient-blind	Patient and investigator-blind	Double-blind
Completeness of follow-up	Y	Y	N
Description of withdrawals	–	–	Y
ITT	–	–	Yes

DM: diabetes mellitus; DPN: diabetic peripheral neuropathy; Y: yes; N: no.
[a] Graded on a scale of 0–5.
[b] Visual analogue scale and NTSS-6-score.

produced more pain relief than TENS therapy only (36% vs. 16.6%).

3.4. *Overall neuropathic symptoms*

In Kumar et al.'s study [8,9], patients were questioned for subjective improvements in overall neuropathic symptoms using scale. TENS therapy was associated with a significantly subjective improvement in overall neuropathic symptoms compared with inactive stimulation [WMD-0.18, 95% CI (−0.32, −0.051)] (Fig. 2).

In addition, Forst et al.'s study [10] showed that more patients in TENS group reported subjective improvement in overall neuropathic symptoms compared with placebo TENS group (70% vs. 29%). Moreover, 100% patients in TENS group would recommend TENS therapy to other patients with the same symptoms of DPN.

3.5. *Sensory nerve thresholds*

Forst et al.'s study [10] evaluated the effectiveness of TENS therapy on sensory nerve thresholds compared with inactive stimulation. It showed that sensory nerve thresholds were comparable between two groups, although there was a tendency towards improvement in the heat, cold and heat pain perception threshold in the TENS group.

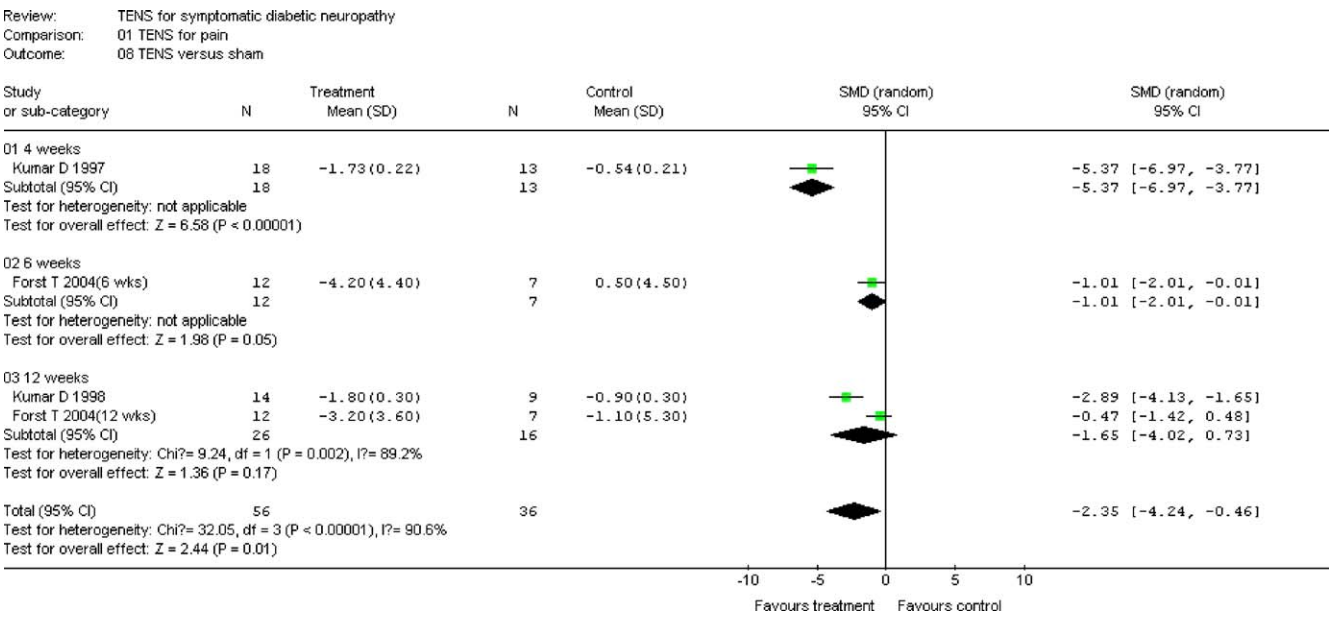


Fig. 1 – Mean pain score reduction.

3.6. *Adverse effects*

TENS was well tolerated and no treatment-related adverse events were registered in TENS group. Kumar et al.'s study [9] reported that 5 patients in placebo TENS group could not tolerate amitriptyline due to amitriptyline-induced sedation, even at a reduced dose of 25 mg/d.

4. Discussion

This meta-analysis demonstrated that TENS therapy had beneficial effect on pain relief in patients with DPN in 6 weeks follow-up and overall neuropathic symptoms in 12 weeks follow-up. TENS therapy was well tolerated and no TENS-related adverse effects were reported in these three RCTs.

TENS therapy was effective in relief of pain in 6 weeks follow-up. Kumar et al. [8,9] reported that 16.6–36% of patients in TENS group even had complete pain relief. Furthermore, TENS therapy was effective in relief of pain in patients who failed to respond to amitriptyline. In addition, TENS in combination with amitriptyline produced more pain relief than TENS therapy alone (36% vs. 16.6%) [9]. This suggested that TENS may be an effective adjunctive therapy for treatment of symptomatic DPN. It is may be due to small sample size that TENS had insignificant effect on pain relief in 12 weeks follow-up. At present, the long-term effect of TENS on pain relief was still controversial. A systematic review, which focused on TENS for chronic pain, indicated that few studies evaluated the long-term analgesic effectiveness of TENS and the long-term effectiveness of TENS in the management of chronic pain was still uncertain [17]. Large multi-centre RCTs are required to assess the long-term effectiveness of TENS in the management of pain related to DPN.

In this study, most participants performed TENS therapy under low frequency stimulation (2–4 Hz). However, the effect of different stimulation parameters of TENS on pain related to DPN has not been studied. Experimental study, which observed the effects of TENS with low frequency (2 Hz) and high frequency (100 Hz) on the chronic inflammatory pain in rats, determined that repeated 100 Hz TENS was more effective on pain relief than that of 2 Hz TENS [18]. A clinical study, which evaluated the effect of the different frequency of the electrical stimulus of TENS on the postoperative pain, illustrated that TENS at mixed (2 Hz and 100 Hz) frequencies of stimulation produced a slightly greater analgesic effect than either low (2 Hz) or high (100 Hz) frequencies alone [19]. It implies that the stimulation frequency played an important role in TENS treatment. A RCT, which evaluated the effects of varying frequency, intensity and stimulation site, of TENS in an experimental model of pain, indicated that only TENS with high frequency and high intensity achieved significantly clinical hypoalgesic effects [20]. It means that the role of TENS frequency and intensity is pivotal to achieving optimal hypoalgesic effects. However, it was inconsistent across trials about the effect of different parameters of TENS on pain. A clinical trial, which examined the optimal stimulation frequency of TENS in reducing pain due to knee osteoarthritis, indicated that 2 weeks of repeated applications of TENS at 2 Hz, 100 Hz or 2/100 Hz produced similar treatment effects for people suffering from osteoarthritic knee [21]. It is still unknown whether there is an optimal stimulation parameter of TENS for pain relief in patients with DPN. Large multi-centre RCTs are needed to evaluate different stimulation parameters of TENS for pain relief in patients with DPN.

The physiological mechanisms whereby TENS relieves pain are uncertain. Experimental study has demonstrated that electrical stimulation could improve endoneurial blood flow and normalize deficits in nerve conduction velocity [22]. Several clinical studies showed that a good clinical response with improvement of peripheral circulation was achieved in the stimulated field, and that may be related to the increased

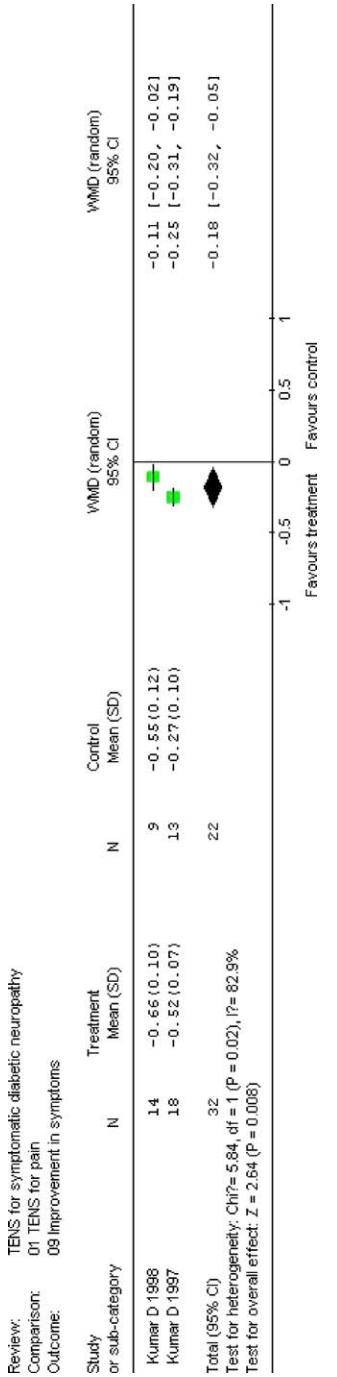


Fig. 2 – Subjective improvement in overall neuropathic symptoms.

endogenous opioid-like substances (e.g. endorphins, encephalin) within the central nervous system [12,23], which inhibit the transmission of painful stimuli by closing the 'gate' to pain transmission by C fibres [24]. A clinical trials, which evaluated the effects of TENS on CO_2 laser evoked potentials in 16 normal subjects, demonstrated that TENS significantly reduced the subjective rating of heat stimuli and the laser evoked potentials amplitude [25]. Forst et al.'s study [10] showed that there was a tendency towards an improvement in the heat, cold and heat pain perception threshold in the TENS group.

Our study reveals that TENS therapy was associated with significantly subjective improvement in overall neuropathic symptoms in 12 weeks follow-up. However, the long-term effect of TENS therapy on overall neuropathic symptoms was still uncertain. Julka et al.'s study [26], which observed the effect of TENS therapy on 82 diabetic patients with neuropathic symptoms, has demonstrated that TENS therapy provided continuous advantage in neuropathic symptoms for average 1.7 years. It means that TENS therapy may have long-term effect on neuropathic symptoms.

TENS therapy was well tolerated and no TENS-related adverse effects were reported in these three RCTs. Forst et al.'s study [10] reported that 100% participants in TENS group would like to recommend TENS therapy to other patients with the same disease. In other clinical trials related to TENS therapy, only a few mild adverse effects such as skin irritation were reported in TENS group [27]. These suggested that as a non-invasive treatment, TENS therapy may be a safe complementary approach in treatment of patients with symptomatic DPN.

The present study has several potential limitations. First, only three RCTs were included in this meta-analysis and the sample size was small. Second, although the patients' baseline has no significantly different, the mean duration of diabetic and DPN was variant in a certain. At the same time, the duration of therapy and the criteria of pain grading were different among trials. Third, two RCTs were performed in the same medical centre. Fourth, publication and language bias may be existed although a comprehensive search was performed. Finally, the long-term efficacy of TENS therapy was still uncertain because the study period was short. We minimized the likelihood of bias and drew objective conclusions as far as possible by developing a detailed protocol in advance, by performing a comprehensive search for published and unpublished trials, by applying explicit methods for study selection, data extraction, and data analysis, and by critically appraising study quality.

5. Conclusions

In conclusion, TENS therapy may be an effective and safe strategy in treatment of symptomatic DPN. The published trials do not provide information on the stimulation parameters which are most likely to provide optimum pain relief, nor do they answer questions about long-term effectiveness. Large multi-centre RCTs, are still warranted to further evaluate the optimal stimulation parameters and long-term effect of TENS on DPN.

Conflict of interests

The authors declare that they have no conflict of interest.

Acknowledgements

We thank Lu Liang from Russian Department of Peking University for his professionally translating a Russian article, and we also thank Chun-yu Du from Harbin Medical University for her help in searching a Russian article.

REFERENCES

[1] M.C. Spruce, J. Potter, D.V. Coppini, The pathogenesis and management of painful diabetic neuropathy: a review, Diabet. Med. 20 (2003) 88–98.
[2] UKPDS Group, Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33), Lancet 352 (1998) 837–853.
[3] A.J. Boulton, G. Knight, J. Drury, J.D. Ward, The prevalence of symptomatic, diabetic neuropathy in an insulin-treated population, Diabetes Care 8 (1985) 125–128.
[4] F. Al-Mahroos, K. Al-Roomi, Diabetic neuropathy, foot ulceration, peripheral vascular disease and potential risk factors among patients with diabetes in Bahrain: a nationwide primary care diabetes clinic-based study, Ann. Saudi Med. 27 (2007) 25–31.
[5] A. Gordois, P. Scuffham, A. Shearer, A. Oglesby, J.A. Tobian, The health care costs of diabetic peripheral neuropathy in the US, Diabetes Care 26 (2003) 1790–1795.
[6] H.J. McQuay, R.A. Moore, C. Eccleston, S. Morley, A.C. Williams, Systematic review of outpatient services for chronic pain control, Health Technol. Assess. 1 (1997) 1–135.
[7] The Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions 4.2.5.
[8] D. Kumar, H.J. Marshall, Diabetic peripheral neuropathy: amelioration of pain with transcutaneous electrostimulation, Diabetes Care 20 (1997) 1702–1705.
[9] D. Kumar, M.S. Alvaro, I.S. Julka, H.J. Marshall, Diabetic peripheral neuropathy: effectiveness of electrotherapy and amitriptyline for symptomatic relief, Diabetes Care. 21 (1998) 1322–1325.
[10] T. Forst, M. Nguyen, S. Forst, B. Disselhoff, T. Pohlmann, A. Pfutzner, Impact of low frequency transcutaneous electrical nerve stimulation on symptomatic diabetic neuropathy using the new Salutaris device, Diabetes Nutr. Metab. 17 (2004) 163–168.
[11] L. Reichstein, S. Labrenz, D. Ziegler, S. Martin, Effective treatment of symptomatic diabetic polyneuropathy by high-frequency external muscle stimulation, Diabetologia 48 (2005) 824–828.
[12] K.M. Ivanov, N.V. Miasnikova, T.I. Ovchinnikova, T.P. Sizova, T.P. Chemezova, The use of transcutaneous electrostimulation in the treatment of diabetic angioneuropathy, Vopr Kurortol Fizioter Lech Fiz Kult (1998) 30–31.
[13] S. Tesfaye, J. Watt, S.J. Benbow, K.A. Pang, J. Miles, I.A. MacFarlane, Electrical spinal-cord stimulation for painful diabetic peripheral neuropathy, Lancet 348 (1996) 1698–1701.
[14] L.G. Claeys, S. Horsch, Transcutaneous oxygen pressure as predictive parameter for ulcer healing in endstage vascular patients treated with spinal cord stimulation, Int. Angiol. 15 (1996) 344–349.
[15] M.A. Hamza, P.F. White, W.F. Craig, E.S. Ghoname, H.E. Ahmed, T.J. Proctor, et al., Percutaneous electrical nerve stimulation: a novel analgesic therapy for diabetic neuropathic pain, Diabetes Care 23 (2000) 365–370.
[16] D.G. Altman, K.F. Schulz, D. Moher, M. Egger, F. Davidoff, D. Elbourne, et al., The revised CONSORT statement for reporting randomized trials: explanation and elaboration, Ann. Intern. Med. 134 (2001) 663–694.
[17] D. Carroll, R.A. Moore, H.J. McQuay, F. Fairman, M. Tramèr, G. Leijon, Transcutaneous electrical nerve stimulation (TENS) for chronic pain, Cochrane Database Syst. Rev. 3 (2001) CD003222.
[18] Y.X. Jiang, Y. Wang, H.X. Liu, Comparison between therapeutic effects of transcutaneous electrical nerve stimulation with the frequency of 2 Hz and 100 Hz on chronic inflammatory pain in rats, Zhongguo Zhong Xi Yi Jie He Za Zhi 21 (2001) 923–925.
[19] M.A. Hamza, P.F. White, H.E. Ahmed, E.A. Ghoname, Effect of the frequency of transcutaneous electrical nerve stimulation on the postoperative opioid analgesic requirement and recovery profile, Anesthesiology 91 (1999) 1232–1238.
[20] L.S. Chesterton, N.E. Foster, C.C. Wright, G.D. Baxter, P. Barlas, Effects of TENS frequency, intensity and stimulation site parameter manipulation on pressure pain thresholds in healthy human subjects, Pain 106 (2003) 73–80.
[21] P.P. Law, G.L. Cheing, Optimal stimulation frequency of transcutaneous electrical nerve stimulation on people with knee osteoarthritis, J. Rehabil. Med. 36 (2004) 220–225.
[22] N.E. Cameron, M.A. Cotter, S. Robertson, Chronic low frequency electrical activation for one week corrects nerve conduction velocity deficits in rats with diabetes of three months duration, Diabetologia 32 (1989) 759–761.
[23] J.S. Han, X.H. Chen, S.L. Sun, X.J. Xu, Y. Yuan, S.C. Yan, et al., Effect of low- and high-frequency TENS on Met-enkephalin-Arg-Phe and dynorphin A immunoreactivity in human lumbar CSF, Pain 47 (1991) 295–298.
[24] D.W. Garrison, R.D. Foreman, Effects of transcutaneous electrical nerve stimulation (TENS) on spontaneous and noxiously evoked dorsal horn cell activity in cats with transected spinal cords, Neurosci. Lett. 216 (1996) 125–128.
[25] M. de Tommaso, P. Fiore, A. Camporeale, M. Guido, G. Libro, L. Losito, et al., High and low frequency transcutaneous electrical nerve stimulation inhibits nociceptive responses induced by CO_2 laser stimulation in humans, Neurosci. Lett. 342 (2003) 17–20.
[26] I.S. Julka, M. Alvaro, D. Kumar, Beneficial effects of electrical stimulation on neuropathic symptoms in diabetes patients, J. Foot Ankle Surg. 37 (1998) 191–194.
[27] R.A. Deyo, N.E. Walsh, D.C. Martin, L.S. Schoenfeld, S. Ramamurthy, A controlled trial of transcutaneous electrical nerve stimulation (TENS) and exercise for chronic low back pain, N. Engl. J. Med. 322 (1990) 1627–1634.