Research article/Raziskovalni prispevek

TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION, PREGABALIN AND THEIR COMBINATION IN PATIENTS WITH PAINFUL DIABETIC NEUROPATHY: EFFECTS ON PAIN AND QUALITY OF LIFE

POVRŠINSKO PROTIBOLEČINSKO ELEKTRIČNO DRAŽENJE, PREGABALIN IN NJUNA KOMBINACIJA PRI BOLNIKIH Z BOLEČO DIABETIČNO NEVROPATIJO: VPLIV NA BOLEČINO IN KAKOVOST ŽIVLJENJA

Metka Moharič,[1, 2] Črt Marinček,[1, 2] Gaj Vidmar,[2, 3] Helena Burger[1, 2]

[1] Institute for Rehabilitation, Republic of Slovenia, Ljubljana, Slovenia
[2] Department of Physical and Rehabilitation Medicine, Faculty of Medicine, University of Ljubljana, Slovenia
[3] Institute of Biostatistics and Biomedical Informatics, Faculty of Medicine, University of Ljubljana, Slovenia

Abstract

Background *Peripheral neuropathy is a common complication of diabetes, whereby pain control is the most difficult issue. The outcomes of existing treatment options are far from satisfactory and the results of studies comparing them are indecisive. Hence, we aimed at comparing the effect of treating pain with transcutaneous electrical nerve stimulation (TENS), pregabalin and their combination in patients with painful diabetic neuropathy (PDN), including the quality-of-life aspect.*

Methods *A randomized clinical trial was planned with 69 PDN patients divided into three equally sized groups receiving TENS, pregabalin or combined treatment. Because of early drop-outs from the pregabalin and combination group due to side effects, randomization was abandoned during recruitment phase and all remaining patients were assigned to TENS, resulting in group sizes of 46, 5 and 14, respectively. Assessments for pain relief and quality of life were performed at baseline, at the end of three-week treatment, and one moth after the end of treatment.*

Results *Observed treatment effects did not differ between the groups. Statistically significant and clinically meaningful reduction of average and worst pain was achieved. Patients rated their quality of life better especially in the bodily pain domain of Short Form-36. One month post treatment, all observed effects were still present. Pain reduction correlated mainly with improvement of physical functioning domain.*

Conclusions *Since TENS did not differ in efficacy from pregabalin and combined treatment, and does not have side effects, it appears to be a viable addition or even alternative to other analgesic modalities in PDN.*

Key words *painful diabetic neuropathy; transcutaneous electrical nerve stimulation; pregabalin; controlled clinical trial; quality of life*

Izvleček

Izhodišča *Periferna nevropatija je pogost zaplet pri sladkorni bolezni, pri katerem je nadzor bolečine izrazito težaven. Obstoječi načini zdravljenja so daleč od idealnih in rezultati raziskav ne*

Corresponding author / Avtorica za dopisovanje:
Metka Moharič, Department of Physical and Rehabilitation Medicine, Linhartova 51, SI-1000 Ljubljana, Slovenia,
Phone +386 1 4758441, Fax +386 1 4376589, E-mail metka.moharic@mf.uni-lj.si

nudijo jasne slike o primerjalni učinkovitosti različnih možnosti. Zato smo želeli primerjati učinek blaženja bolečine s površinskim protibolečinskim električnim draženjem (TENS), pregabalinom in njuno kombinacijo pri bolnikih z bolečo diabetično nevropatijo (PDN), vključno s kakovostjo življenja.

Metode *Načrtovali smo randomiziran klinični poskus z 69 bolniki s PDN, razdeljenimi v tri enako velike skupine, zdravljene s TENS, pregabalinom ali njuno kombinacijo. Zaradi zgodnjih izstopov iz skupin zdravljenih s pregabalinom in kombinacijo smo randomizacijo opustili in vse nadaljnje bolnike vključili v skupino s TENS, tako da je bilo končno število preiskovancev v omenjenih treh skupinah 46, 5 in 14. Bolečino in kakovost življenja smo ocenili ob vstopu v raziskavo, po koncu trotedenskega zdravljenja in en mesec po zaključenem zdravljenju.*

Rezultati *Opaženi učinki zdravljenja se med skupinami niso razlikovali. Doseženo je bilo statistično značilno in klinično pomembno zmanjšanje povprečne in najhujše bolečine. Bolniki so svojo kakovost življenja ocenili kot boljšo zlasti na lestvici telesne bolečine Kratkega vprašalnika o zdravju SF-36. Vsi opaženi učinki so bili mesec dni po zdravljenju še vedno prisotni. Zmanjšanje bolečine je bilo povezano predvsem z izboljšanjem kakovosti življenja na področju telesnega delovanja.*

Zaključki *Ker se učinkovitost TENS ne razlikuje od pregabalina in kombiniranega zdravljenja, hkrati pa nima neželenih učinkov, je TENS lahko primerno dopolnilo ali celo nadomestilo drugim načinom blaženja bolečine pri PDN.*

Ključne besede *boleča diabetična nevropatija; površinsko protibolečinsko električno draženje; pregabalin; nadzorovan klinični poskus; kakovost življenja*

Introduction

Peripheral diabetic neuropathy is a common complication of diabetes affecting up to 45% of patients with diabetes.[1] Forty-five percent of patients have pain longer than one year.[2] The presentation and character of pain in painful diabetic neuropathy (PDN) can be highly diverse. However, they typically worsen at night. Patients describe the pain as burning, pins and needles, shooting, aching, jabbing, sharp, cramping, tingling and cold. In addition, they may experience allodynia (pain response to a stimulus not normally associated with pain in nature). When pain is not adequately controlled, mood and sleep disturbances are common.[3]

Control of pain constitutes one of the most difficult management issues in PDN. Despite the considerable increase in the number of randomized placebo-controlled trials, the medical treatment of neuropathic pain is still far from being satisfactory.[4, 5] Available treatment options generally do not provide total relief[6] nor are they effective in all patients.[7] Several pharmacologic symptomatic treatments are available, such as analgesics, antidepressants, anticonvulsants with analgesic profile, dual inhibitor of serotonin and norepinephrine reuptake, serotonin receptor inhibitors, narcotic analgesics, non-steroidal anti-inflammatory drugs and topical therapies. Pregabalin is a selective, high-affinity ligand for the α_2-δ subunit of voltage-gated calcium channels,[8] which are thought to play an important role in modulating neuropathic pain.[9, 10] Ancillary treatments that are harmless are often used. Non-pharmacological treatments include nerve stimulation therapies, electrical spinal cord stimulation, and counselling or other psychological treatments. Nerve stimulation therapies used in PDN are transcutaneous electrical nerve stimulation (TENS), percutaneous electrical nerve stimulation (PENS) and acupuncture.[11] TENS is the application of electrical stimulation of varying frequency, intensity and pulse duration to the skin for pain relief.[12] It is a commonly used nonpharmacologic and non-invasive treatment for pain. Its analgesic mechanisms probably involve gate control theory,[13] physiological block,[14] and endogenous pain inhibitory system.[15]

Unfortunately, there is no definite evidence for or against the effectiveness of TENS in the management of chronic pain. Many studies judge TENS to have had an overall positive effect on pain, but only few of them are of good methodological quality, so additional trials are needed to confirm its effectiveness. Thus the aim of our study was to assess the impact of treating pain with TENS, pregabalin and their combination on perceived pain and quality of life in patients with PDN in an effort to obtain data that may be used to guide clinical practice and future treatment research.

Methods

Patients

We intended to include 60 patients into three equally sized groups of pregabalin, TENS and combination thereof, and foresaw 9 reserves because of possible drop-out. Patients with diabetes mellitus type in stable glycaemic control and with typical neuropathic symptoms such as tingling, burning and shooting pain, often nocturnal exacerbations, for at least 6 months,

principally affecting the lower limbs, who had agreed with at least 2 answers in the Michigan Neuropathy Screening Instrument (MNSI)[16] were recruited from the outpatient diabetic foot clinic. MNSI is a simple questionnaire, which consists of 15 yes/no questions on foot sensation (pain, numbness and sensitivity to temperature), including one relevant to general asthenia and one relevant to peripheral vascular disease. A score above 2 accurately identifies patients with diabetic neuropathy.[16] Patients with known other forms of neuropathy, significant pain of alternate aetiology or peripheral vascular disease were excluded. In all patients, small fibre neuropathy with abnormal function of C an Aδ fibres had been confirmed with quantitative sensory testing (TSA 2001 Thermal Sensory Analyser, Medoc Ltd, Ramat Yishai, Israel). All patients were Slovenian citizens.

Patients were to be randomly assigned to one of the three treatment groups according to a randomization list generated without blocking. The protocol was approved by the National Medical Ethics Committee of the Republic of Slovenia and each patient enrolled was informed about the trial and its risks and gave written informed consent before participating in the study.

The actual study design differed from the planned since by the time when 8 patients had been recruited into the pregabalin group, 15 into the combination group and 9 into the TENS group, 3 patients in the pregabalin group had reported serious side effects that made them withdraw from the study in the first three or four days, 1 patient with combined treatment had withdrawn from the study because of a side-effect related accident, and 6 patients with combined treatment had also reported some kind of side effect. Therefore, it was decided that all the remaining patients, including the 9 reserves, would be recruited into the TENS group. The change in the protocol was approved by the National Medical Ethics Committee. The path of recruitment is shown in Figure 1.

Interventions

Transcutaneous electrotherapy was given by a portable, dual channel unit (Mediotens, Iskra Medical, Ljubljana, Slovenia) that generates direct current with pulse widths of 30 to 260 μs, intensity 0 to 14 mA, frequency 2 to 150 Hz in constant, burst or modulated form. The standard TENS parameters were used (rectangular, constant, monophasic impulse; frequency 100 Hz; impulse width 0.2 ms). Electrodes (self-adhesive, size 5×5 cm PALS electrodes, Axelgaard, Fallbrook, CA, USA) were placed on both legs at the same time proximally about 10 centimetres above the internal or external malleolus and distally on the sole or dorsum of the foot, alternating the two configurations each day (see Figure 2). Each patient was individually instructed on how to place the electrodes and how to use the stimulator. It was explained to each patient which electrical sensations should be felt (mild paresthesias), and which intensity to use in case of impaired sensation/perception thresholds. The treatment process was demonstrated, thereby providing experience and feeling of the electrodes. The TENS stimulator was then loaned to the patient for home use, where it was applied for three consecutive hours daily for three weeks.

Pregabalin was given 2 × 75 mg/day during the first week and then 2 × 150 mg/day for two weeks. After

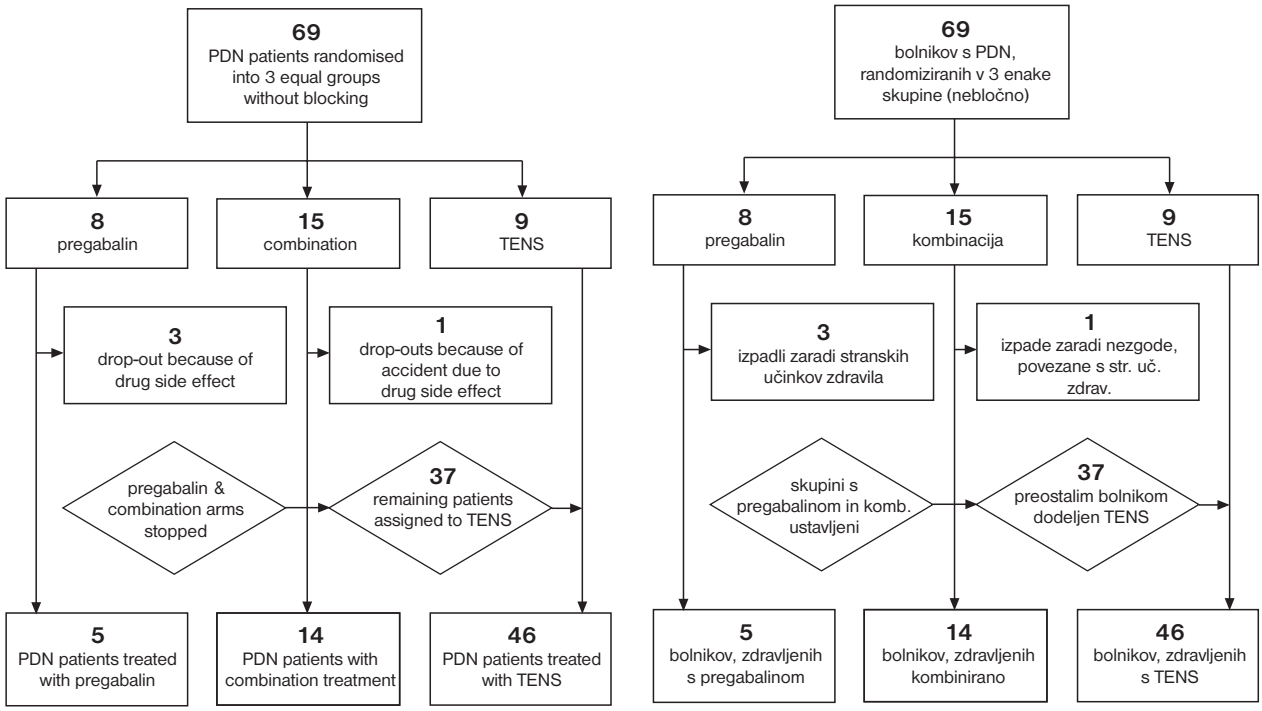

Figure 1. *Paths of the patients and their assignment to groups in the trial.*

Sl. 1. *Poti bolnikov v kliničnem poskusu in njihovo vključevanje v skupine.*

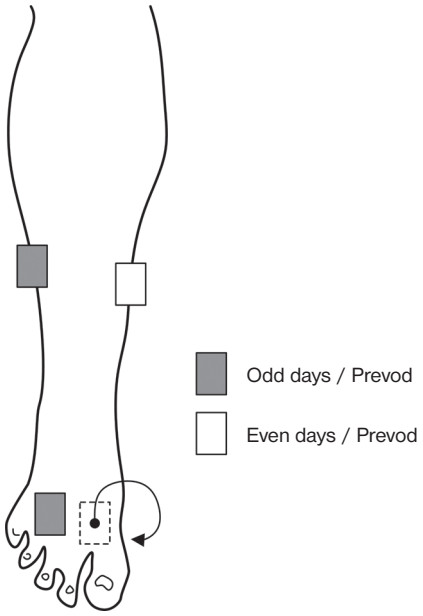

Figure 2. *Placement of TENS electrodes (because the dual channel unit was used, the electrodes were placed in that pattern on both lower limbs at the same time; the distal electrode was placed on the sole on the even days and on the dorsum of the foot on the odd days).*

Sl. 2. *Namestitev elektrod za TENS (ker smo uporabili dvokanalni stimulator, so bile elektrode na ta način nameščene na oba spodnja uda hkrati; lihe dni je bila distalna elektroda nameščena na podplatu, sode dni pa na nartu).*

that, it was reduced to 2 × 75 mg/day for one week, and then completely withdrawn. In the combination group, both agents were used in combination in the same way as in the first two groups.

Other various drugs, physical therapies and complementary remedies for the relief of neuropathic pain were prohibited 10 days prior to and during the study, including one month post treatment. Patients were allowed to continue on antidepressant (TCAs and selective serotonin reuptake inhibitors). Existing treatment with aspirin (up to 300 mg/day) for cardiovascular prophylaxis was permitted and patients were also permitted to take paracetamol for the treatment of conditions other than neuropathic pain. Since none of the patients was receiving a therapy for neuropathic pain, the washout period was not necessary.

Outcomes

Measurements were done at baseline, at the end of treatment (i.e., after three weeks), and one month after the end of treatment. Average and worst pain intensity, unpleasantness and its interference with daily activities and sleep were assessed using four 100 mm horizontal visual analogue scales (VASs). Quality of life was assessed using Medical Outcome Study Short Form-36 Health Survey (SF-36).[17] The SF-36 is a well validated self-reported questionnaire assessing health-related QOL within 8 domains: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role and mental health. The questionnaire takes only a few minutes to complete, requiring responses to 36 simple questions that are scored and combined to represent the abovementioned QOL domains. These domain scores are presented as values on a 0–100 scale, with larger values representing better QOL.

Data Analysis

The planned sample size of 20 patients in each group was calculated on the basis of one-way analysis of variance (ANOVA) so that if TENS had no effect (therefore the average change in that group would be zero) and the average relative improvement in the pregabalin group (and hence also in the combination group) were 30% (thus yielding the standard deviation of group means of 0.14, while the common standard deviation of the three groups was assumed to be 0.3), the sample would achieve 90% power to detect the differences among the means versus the alternative of equal means with a 0.05 significance level. The sample size calculation was performed using PASS 2008 (J. Hintze, 2008, Kaysville, Utah, www.ncss.com).

Because randomization was not followed throughout patient recruitment, the groups were tested regarding equality of baseline characteristics using ANOVA for numeric variables and Fisher's exact test for categorical variables.

Relative change from baseline was computed for all outcomes at the end of treatment, whereby baseline score was subtracted from the score at the end of treatment for SF-36 domains, and vice versa for pain scores, so that a positive change score indicated improvement on both types of scales. To allow for computation of relative change, 0.5 was substituted for the baseline value in cases of zero baseline value.

Because of asymmetric distributions and/or limited range of the outcome measures and their relative change scores, nonparametric statistical methods were used for their analyses. For comparing change between groups, exact Kruskal-Wallis test was used. For testing change over time, exact Friedman test was used with exact Wilcoxon matched-pairs signed-rank test using Bonferroni correction as post-hoc tests. Spearman's rank-correlation (ρ) was used to assess associations (monotonous, but not necessarily linear) between change in pain intensity and change in SF-36 domains scores, whereby positive correlations were expected because a positive change score indicated improvement on both types of scales. The proportion of patients with at least 30% relative improvement in each outcome measure was compared between groups using extended Fisher's exact test.

All statistical tests were two-sided. Significance level was set at 5%. Statistical analyses were performed using SPSS 15.0 for Windows (Chicago, IL, 2007).

Results

Patients' characteristics are summarized in Table 1. Since gender should not have influenced the results of treatment, potentially important imbalance between

Table 1. *Patients' characteristics (group comparison and total sample).*

Tab. 1. *Značilnosti bolnikov (primerjava skupin in celotni vzorec).*

Treatment Zdravljenje	TENS TENS (N = 46)	Pregabalin Pregabalin (N = 5)	Combined Kombinirano (N = 14)	Unadjusted Nepopravljeni *p*	Total sample Celotni vzorec (N = 65)	
Numeric data Številski podatki	Mean (SD) Povpr. (SO)	Mean (SD) Povpr. (SO)	Mean (SD) Povpr. (SO)	(ANOVA) (ANOVA)	Mean (SD) Povpr. (SO)	Me (range) Me (razpon)
Age (years) Starost (leta)	62.4 (6.5)	63.4 (7.2)	60.6 (6.4)	0.590	62.1 (6.5)	62.0 (43–75)
MNSI MNSI	6.6 (1.9)	8.2 (1.9)	8.0 (1.6)	0.022	7.0 (1.9)	7.0 (2–12)
Disease duration (yrs) Trajanje bolezni (leta)	17.0 (9.5)	15.4 (8.4)	19.6 (7.8)	0.557	17.5 (9.0)	15.0 (2–36)
Pain duration (yrs) Trajanje bolečine (leta)	4.9 (4.6)	3.2 (1.8)	6.7 (3.7)	0.228	5.2 (4.3)	4.5 (1–20)
GlcK (mmol/l) GlcK (mmol/l)	8.3 (2.3)	8.0 (1.8)	7.6 (1.8)	0.627	8.1 (2.1)	7.6 (4–15)
HbA1c (%) HbA1c (%)	7.6 (1.0)	8.3 (0.9)	8.1 (1.0)	0.099	7.7 (1.0)	7.7 (6–11)
Urea (mmol/l) Sečnina (mmol/l)	6.1 (1.3)	5.6 (1.0)	5.7 (2.0)	0.549	6.0 (1.4)	5.7 (2–9)
Creatinin (mmol/l) Kreatinin (mmol/l)	84.2 (17.2)	65.2 (15.0)	83.4 (18.1)	0.072	82.5 (17.7)	81.0 (48–133)
GlcU (U/l) GlcU (U/l)	0.3 (0.8)	0.4 (0.9)	0.6 (1.2)	0.485	0.4 (0.9)	0.0 (0–4)
Categorical data Opisni podatki	N Št.	N Št.	N Št.	(exact test) (eksaktni test)	N (%) Št. (%)	
Gender (male/female) Spol (M/Ž)	25 / 21	0 / 5	8 / 6	0.080	33 (51%) / 32 (49%)	
DM treatment Zdravljenje SB				0.547		
diet dieta	2	0	0		2 (3%)	
OHA OHA	17	1	4		22 (34%)	
insulin inzulin	21	4	10		35 (54%)	
OHA+insulin OHA+inzulin	6	0	0		6 (9%)	

SD = standard deviation; Me = median; OHA = oral hypoglycaemic agents.

ANOVA = enosmerna analiza variance za neponovljene meritve; MNSI = presejalni vprašalnik nevropatije; SB = sladkorna bolezen; SO = standardni odklon; Me = mediana; OHA = hipoglikemična zdravila za oralno uporabo.

groups appeared only regarding MNSI (with somewhat lower scores in the TENS group). The Bonferroni correction for multiple tests (resulting in critical observed *p* for significance at 5% level of 0.05/11≈0.005, which is also the critical value for the lowest observed *p* using the Holm correction) showed that difference is not statistically significant. For this reason, because of sample size constraints, and also because the difference between the groups in average MNSI of about 1 point is not clinically meaningful, no adjustments for baseline covariates were made in subsequent group comparisons.

The VAS scores, together with percentage change from baseline and results of statistical analysis, are reported in Table 2. For the pregabalin group, variability estimates (interquartile range or other) of relative change are not sensible because of small group size and probable bias due to drop-out, so they are not reported, and the same applies to statistical inference within that group. In the TENS group and the total sample, statistically significant reduction of average and worst pain intensity, unpleasantness and interference with sleep was observed, whereby worst pain intensity and unpleasantness were even further reduced one month after treatment. In the combined treatment group, the effects were similar, though less pronounced regarding pain unpleasantness and interference with sleep, but more pronounced regarding interference with daily activities.

The SF-36 scores and the results of their analyses are presented in Table 3. As in Table 2, only medians are reported for relative change in the pregabalin group, and statistical tests of difference between time-points are omitted within that group. In the TENS group, the combined treatment group and the total sample, statistically significant change in SF-36 scores was detected in the bodily pain domain, which the patients rated better after the treatment, while one month after the treatment the scores in that domain remained similar. In the combined treatment group and the total sample, improvement in general health was also statistically significant, though smaller. The scores of other SF-36 domains also tended to improve after treatment, but the changes were not statistically significant.

Table 2. *Descriptive statistics and results of statistical tests for visual analogue scale scores.*
Tab. 2. *Opisne statistike in rezultati statističnih testov za vidne analogne lestvice.*

			Baseline Začetek zdravljenja	At the end of treatment Konec zdravljenja	One month post treatment Meseci dni po koncu zdravljenja	Relative drop from baseline to end of treatment Relativno zmanjš. od zač. do konca zdravljenja	Comparison between time points Primerjava med časovnimi točkami
TENS TENS	Average pain Povpr. bol.	Intensity* / Jakost*	46 (29, 61)	25 (4, 46)	17 (4, 44)	51% (–5%,92%)	1 > 2, 3
		Unpleasantness* / Neprijetnost*	58 (31, 73)	29 (5, 52)	13 (3, 45)	41% (–7%,89%)	1 > 2, 3
		Interf. with DA* / Motenje DA*	14 (3, 39)	7 (1, 35)	6 (2, 29)	7% (–38%,79%)	NS
		Interf. with sleep* / Motenje spanja*	41 (13, 71)	14 (2, 42)	9 (2, 50)	38% (–13%,84%)	1 > 2, 3
	Worst pain Najhujša bolečina	Intensity* / Jakost*	73 (47, 88)	50 (35, 79)	39 (10, 70)	13% (–1%,37%)	1 > 2 > 3
		Unpleasantness* / Neprijetnost*	77 (53, 90)	52 (32, 76)	36 (7, 64)	18% (–1%,47%)	1 > 2 > 3
		Interf. with DA* / Motenje DA*	30 (7, 67)	28 (3, 64)	24 (4, 53)	–2% (–51%,32%)	NS
		Interf. with sleep* / Motenje spanja*	59 (25, 88)	35 (6, 65)	24 (5, 61)	17% (–13%,66%)	1 > 2, 3
Pregabalin Pregabalin	Average pain Povpr. bol.	Intensity / Jakost	64 (51, 84)	43 (10, 56)	42 (35, 91)	53%	NA
		Unpleasantness / Neprijetnost	70 (59, 89)	43 (10, 54)	48 (34, 91)	54%	NA
		Interf. with DA / Motenje DA	57 (11, 86)	25 (13, 62)	47 (34, 68)	16%	NA
		Interf. with sleep / Motenje spanja	68 (38, 89)	9 (4, 54)	67 (22, 95)	80%	NA
	Worst pain Najhujša bolečina	Intensity / Jakost	88 (56, 92)	69 (60, 87)	71 (51, 98)	2%	NA
		Unpleasantness / Neprijetnost	87 (64, 98)	71 (64, 83)	70 (45, 98)	3%	NA
		Interf. with DA / Motenje DA	61 (53, 97)	54 (42, 77)	57 (41, 83)	11%	NA
		Interf. with sleep / Motenje spanja	91 (41, 97)	50 (24, 80)	87 (57, 98)	33%	NA
Combined treatm. Kombinir. zdravlj.	Average pain Povpr. bol.	Intensity* / Jakost*	42 (31, 51)	22 (16, 49)	36 (21, 66)	41% (3%,56%)	1 > 2, 3
		Unpleasantness / Neprijetnost	49 (37, 54)	37 (23, 67)	43 (29, 66)	8% (–62%,47%)	NS
		Interf. with DA / Motenje DA	43 (20, 66)	35 (6, 68)	31 (16, 70)	2% (–11%,56%)	NS
		Interf. with sleep / Motenje spanja	57 (24, 78)	31 (7, 55)	53 (16, 72)	41% (–27%,91%)	NS
	Worst pain Najhujša bolečina	Intensity* / Jakost*	75 (71, 89)	64 (44, 78)	60 (34, 76)	16% (–8%,47%)	1 > 2, 3
		Unpleasantness / Neprijetnost	71 (53, 78)	61 (38, 80)	67 (40, 79)	7% (–15%,25%)	NS
		Interf. with DA* / Motenje DA*	62 (32, 91)	48 (8, 78)	43 (24, 74)	10% (–13%,51%)	1 > 2, 3
		Interf. with sleep / Motenje spanja	86 (30, 95)	56 (44, 78)	79 (26, 87)	20% (4%,49%)	NS
Total sample Celotni vzorec	Average pain Povpr. bol.	Intensity* / Jakost*	46 (30, 61)	23 (6, 46)	24 (7, 47)	52% (–5%,89%)	1 > 2, 3
		Unpleasantness* / Neprijetnost*	55 (34, 70)	29 (6, 55)	28 (7, 51)	35% (–9%,85%)	1 > 2, 3
		Interf. with DA / Motenje DA	20 (5, 48)	16 (2, 46)	12 (3, 40)	4% (–25%,74%)	NS
		Interf. with sleep* / Motenje spanja*	44 (18, 76)	15 (3, 50)	22 (4, 62)	49% (–12%,88%)	1 > 2, 3
	Worst pain Najhujša bolečina	Intensity* / Jakost*	74 (52, 89)	58 (39, 79)	46 (18, 76)	13% (–3%,35%)	1 > 2 > 3
		Unpleasantness* / Neprijetnost*	75 (56, 89)	54 (37, 78)	43 (16, 73)	12% (–4%,40%)	1 > 2 > 3
		Interf. with DA / Motenje DA	45 (11, 83)	33 (6, 71)	32 (7, 70)	0% (–36%,41%)	NS
		Interf. with sleep* / Motenje spanja*	67 (30, 92)	43 (16, 78)	38 (7, 80)	17% (–1%,63%)	1 > 2, 3

Data are reported as median (1st quartile, 3rd quartile); for pregabalin group, only median relative drop is reported. * p<0.05 from Friedman test for difference between time-points. Comparisons between time-points (1 = baseline; 2 = at the end of treatment; 3 = one month post treatment) indicate significant differences from Wilcoxon tests with Bonferroni correction; NS = not significant; NA = not applicable. DA = daily activities.

Podatki so navedeni kot mediana (1., 3. kvartil); za skupino s pregabalinom je navedena le mediana relativnega zmanjšanja. * p<0.05 p<0.05 za Friedmanov test razlik med časovnimi točkami. Primerjave med časovnimi točkami (1 = zač. zdravljenja; 2 = konec zdr.; 3 = mesec dni po zdr.) označujejo statistično značilne razlike glede na Wilcoxonov test z Bonferronijevim popravkom; NS = ni stat. značilno; NA = ni izvedljivo. DA = dnevne aktivnosti.

No difference was found between groups regarding relative change either in VAS scores or in SF-36 domains (unadjusted *p* ranging between 0.174 and 0.978). For another comparison of treatment effects between groups, we adopted the definition of respondents to treatment as the patients reporting at least 30% improvement in the outcome measures, as it has been suggested for pain (18). The share of such patients is reported in Table 4 for each group and for the total sample, whereby proportions can only be meaningfully estimated and reported for the total sample. Again, no significant differences were found between group either regarding average and worst pain, or regarding SF-36 domains.

The data reported in Table 4 confirm that the relative improvement was the smallest regarding quality of life (9–27% of responders in various domains in the total sample, 25% of them on average across domains), larger regarding worst pain (17–29% of responders on various scales, 33% of them on average across scales), and the largest regarding average pain (40–55% of responders on various scales, 50% of them on average across scales).

Correlations between relative improvement in SF-36 domains and pain scores are listed in Table 5. Because of absence of differences between groups, they were computed for the total sample. Reductions on VAS scales correlated most notably with vitality, and also with the physical and social functioning domains of SF-36. Additionally, reduction of worst pain unpleasantness and interference with daily activities correlated with improved physical role, and reduction of average pain interference with daily activities correlated with improvement in mental health domain. All statistically significant correlations were positive, with ρ values ranging between 0.25 and 0.44.

Side Effects

As already indicated in the Methods section, three patients in the pregabalin group experienced such severe somnolence and dizziness that they had to withdraw

Table 3. *Descriptive statistics and results of statistical tests for SF-36 scores.*

Tab. 3. *Opisne statistike in rezultati statističnih testov za Kratki vprašalnik o zdravju SF-36.*

	SF-36 domain	Baseline	At the end of treatment	One month post treatment	Relative raise from baseline to end of treatm.	Comparison between time-points
	Podlestvica SF-36	Začetek zdravljenja	Konec zdravljenja	Meseci dni po koncu zdravljenja	Relativno poveč. od zač. do konca zdravljenja	Primerjava med časovnimi točkami
TENS TENS	PF – Physical funct. / PF – telesno delovanje	65 (50, 81)	68 (45, 90)	78 (54, 85)	0% (–13%,13%)	NS
	RP – Physical role / RP – telesna vloga	75 (0, 100)	88 (19, 100)	75 (25, 100)	0% (0%,33%)	NS
	RE – Emotional role / RE – čustvena vloga	100 (33, 100)	100 (33, 100)	100 (33, 100)	0% (0%,12%)	NS
	BP – Bodily pain * / BP – telesna bolečina *	41 (31, 61)	61 (41, 74)	62 (41, 74)	23% (0%,51%)	1 < 2, 3
	VI – Vitality / VI – vitalnost	55 (50, 61)	58 (44, 71)	58 (40, 75)	4% (–18%,33%)	NS
	MH – Mental health / MH – duševno zdravje	68 (56, 80)	68 (56, 80)	70 (52, 84)	0% (–13%,14%)	NS
	SF – Social funct. / SF – socialno delovanje.	75 (59, 91)	75 (50, 100)	75 (63, 88)	0% (–19%,20%)	NS
	GH – General health / GH – splošno zdravje	39 (29, 62)	41 (29, 63)	49 (35, 62)	0% (–12%,25%)	NS
Pregabalin Pregabalin	PF – Physical funct. / PF – telesno delovanje	45 (25, 50)	40 (20, 68)	35 (13, 48)	0%	NA
	RP – Physical role / RP – telesna vloga	50 (13, 75)	50 (25, 50)	50 (13, 50)	–33%	NA
	RE – Emotional role / RE – čustvena vloga	67 (17, 83)	67 (17, 100)	33 (0, 67)	0%	NA
	BP – Bodily pain / BP – telesna bolečina	31 (27, 37)	41 (22, 58)	31 (22, 46)	24%	NA
	VI – Vitality / VI – vitalnost	50 (40, 58)	40 (40, 63)	30 (25, 38)	–17%	NA
	MH – Mental health / MH – duševno zdravje	56 (50, 68)	68 (50, 80)	44 (36, 60)	12%	NA
	SF – Social funct. / SF – socialno delovanje.	63 (50, 81)	75 (63, 75)	63 (44, 69)	20%	NA
	GH – General health / GH – splošno zdravje	30 (30, 35)	40 (20, 55)	25 (18, 38)	0%	NA
Combined treatment Kombinirano zdravljenje	PF – Physical funct. / PF – telesno delovanje	38 (24, 66)	53 (29, 76)	55 (29, 75)	0% (0%,41%)	NS
	RP – Physical role / RP – telesna vloga	38 (0, 50)	38 (0, 75)	38 (0, 75)	0% (–13%,100%)	NS
	RE – Emotional role / RE – čustvena vloga	33 (0, 100)	67 (0, 100)	50 (0, 100)	0% (0%,200%)	NS
	BP – Bodily pain / BP – telesna bolečina	37 (22, 51)	41 (22, 54)	41 (29, 62)	0% (–2%,43%)	NS
	VI – Vitality / VI – vitalnost	48 (40, 51)	45 (24, 61)	40 (20, 58)	–10% (–44%,18%)	NS
	MH – Mental health / MH – duševno zdravje	58 (43, 84)	68 (42, 81)	60 (34, 84)	0% (–6%,12%)	NS
	SF – Social funct. / SF – socialno delovanje.	63 (38, 75)	69 (25, 88)	56 (34, 75)	0% (–33%,18%)	NS
	GH – General health * / GH – splošno zdravje *	30 (15, 45)	30 (14, 55)	33 (20, 51)	16% (–8%,51%)	1 < 2, 3
Total sample Celotni vzorec	PF – Physical funct. / PF – telesno delovanje	60 (40, 785)	65 (38, 85)	65 (40, 80)	0% (–9%,19%)	NS
	RP – Physical role / RP – telesna vloga	50 (0, 100)	50 (0, 100)	50 (25, 100)	0% (0%,33%)	NS
	RE – Emotional role / RE – čustvena vloga	67 (33, 100)	100 (17, 100)	67 (17, 100)	0% (0%,50%)	NS
	BP – Bodily pain * / BP – telesna bolečina *	41 (26, 51)	51 (31, 74)	52 (32, 62)	22% (0%,48%)	1 < 2, 3
	VI – Vitality / VI – vitalnost	50 (45, 60)	55 (40, 70)	50 (35, 70)	0% (–26%,32%)	NS
	MH – Mental health / MH – duševno zdravje	64 (56, 80)	68 (54, 80)	68 (48, 82)	0% (–9%,14%)	NS
	SF – Social funct. / SF – socialno delovanje.	62 (50, 88)	75 (50, 88)	75 (50, 88)	0% (–21%,20%)	NS
	GH – General health * / GH – splošno zdravje *	35 (25, 54)	40 (25, 61)	45 (28, 60)	0% (–12%,27%)	1 < 2, 3

Data are reported as median (1st quartile, 3rd quartile); for pregabalin group, only median relative raise is reported. * p<0.05 from Friedman test for difference between time-points. Comparisons between time-points (1 = baseline; 2 = at the end of treatment; 3 = one month post treatment) indicate significant differences from Wilcoxon tests with Bonferroni correction; NS = not significant; NA = not applicable.

Podatki so navedeni kot mediana (1., 3. kvartil); za skupino s pregabalinom je navedena le mediana relativnega povečanja. * p<0.05 za Friedmanov test razlik med časovnimi točkami. Primerjave med časovnimi točkami (1 = zač. zdravljenja; 2 = konec zdr.; 3 = mesec dni po zdr.) označujejo statistično značilne razlike glede na Wilcoxonov test z Bonferronijevim popravkom; NS = ni stat. znač.; NA = ni izvedljivo.

Table 4. *Share of patients with at least 30% improvement in outcome measures (comparison between groups and estimate for the total sample).*

Tab. 4. *Delež bolnikov z izboljšanjem izida za najmanj 30 % (primerjava med skupinami in ocena za celotni vzorec).*

Treatment	TENS	Pregabalin	Combined	Unadjusted	Total sample
Zdravljenje	TENS (N = 46)	Pregabalin (N = 5)	Kombinirano (N = 14)	Nepopravljeni *p*	Celotni vzorec (N = 65)
Average pain / Povprečna bolečina					
Intensity / Jakost	26	3	7	0.917	36 (55%)
Unpleasantness / Neprijetnost	26	3	5	0.390	34 (52%)
Interference with DA / Motenje DA	20	1	5	0.654	26 (40%)
Interference with sleep / Motenje spanja	23	4	7	0.502	34 (52%)
Worst pain / Najhujša bolečina					
Intensity / Jakost	13	0	4	0.519	17 (26%)
Unpleasantness / Neprijetnost	16	1	3	0.603	20 (31%)
Interference with DA / Motenje DA	12	2	6	0.485	20 (31%)
Interference with sleep / Motenje spanja	20	3	6	0.840	29 (45%)
SF-36 domain / Podlestvica SF-36					
PF – Physical functioning / PF – telesno delovanje	7	1	5	0.210	13 (20%)
RP – Physical role / RP – telesna vloga	13	1	6	0.539	20 (31%)
RE – Emotional role / RE – čustvena vloga	11	2	4	0.721	17 (26%)
BP – Bodily pain / BP – telesna bolečina	22	1	4	0.305	27 (42%)
VI – Vitality / VI – vitalnost	15	1	3	0.737	19 (29%)
MH – Mental health / MH – duševno zdravje	8	0	2	0.864	10 (15%)
SF – Social functioning / SF – socialno delovanje	8	0	1	0.597	9 (14%)
GH – General health / GH – splošno zdravje	8	2	5	0.185	15 (23%)

DA = daily activities. / DA = dnevne aktivnosti.

Table 5. *Rank-correlations between relative improvement in SF-36 domains and pain scores for the total sample.*

Tab. 5. *Korelacije rangov med relativnim izboljšanjem na podlestvicah SF-36 in bolečinskimi lestvicami za celotni vzorec.*

SF-36 domain / Podlestvica SF-36	Average pain / Povprečna bolečina				Worst pain / Najhujša bolečina			
	Intensity / Jakost	Unpleasantness / Neprijetnost	Interference with sleep / Motenje spanja	Interference with DA / Motenje DA	Intensity / Jakost	Unpleasantness / Neprijetnost	Interference with sleep / Motenje spanja	Interference with DA / Motenje DA
PF	0.26 *	0.06	0.18	0.10	0.13	0.17	0.25 *	0.28 *
RP	0.06	–0.02	0.07	–0.01	0.20	0.26 *	0.29 *	0.05
RE	0.18	0.01	0.05	0.01	0.19	0.09	0.18	0.12
BP	0.16	–0.02	0.13	0.05	0.08	–0.09	0.21	–0.05
VI	0.30 *	0.21	0.25 *	0.29 *	0.30 *	0.44 *	0.16	0.28 *
MH	0.05	0.02	0.25 *	0.17	0.18	0.19	0.21	0.04
SF	0.26 *	0.17	0.13	0.19	0.29 *	0.29 *	0.23	0.17
GH	0.02	0.00	0.07	0.09	0.17	0.09	0.16	0.19

DA = daily activities; * p<0.05.
DA = dnevne aktivnosti; * p<0.05.

from the study. Complaints in the combined group beside somnolence and dizziness included peripheral oedema, weight gain, elevated blood glucose values and withdrawal headache, while one patient from the combined group withdrew from the study because of a traffic accident (tractor overturning) caused by somnolence induced (with all likelihood) by pregabalin. In the TENS group, none of the patients reported any local or systemic side effects, neither did they report any problems with continuous TENS application for three hours daily.

Discussion

To our knowledge, this is the first study comparing efficacy of nerve stimulation and pharmacological treatment of pain in painful diabetic neuropathy. Our intention was to assess efficacy of TENS because the methodological quality of the studies in this area is relatively low. As medical knowledge accumulates, randomized placebo controlled trials should become infrequent, because when an efficacious treatment already exists, it is unethical to assign placebo treatment to patients.[19] In such situations, one solution is to use an existing drug for the same disease as an active comparator in an equivalence trial.[19] We followed that approach until the withdrawal of three patients in the pregabalin arm, after which we opted for the solution that appeared the most ethical and scientifically valid given the available evidence.[20]

Assessment after three weeks and one month afterwards ensured validity of the comparison between treatments, because gradual introduction and withdrawal of pregabalin is in accordance with the treatment recommendations,[21–23] whereby the last week is not clinically considered as treatment, while the three weeks until the last assessment provided a sufficient wash-out period.

In real life, a sufficient level of pain relief is probably one that allows the patient to have an acceptable quality of life.[11] According to Farrar et al.,[18] a change in pain scores of 30% is clinically meaningful. Others report a 50% change in pain score as a meaningful improvement,[24] but if we consider as "responders" to treatment those patients who report pain relief above 50%, then based on most recent reviews and the European Federation of Neurological Science guidelines only 30-40% of the patients with chronic neuropathic pain achieve that target with pharmacotherapy.[5, 25] The 50% rule is being increasingly contested also because in many patients, objective markers of satisfactory improvement may co-exist with nominal levels of scaled pain relief much below 50%.[26] Therefore, we chose the 30% criterion.

The reductions in VAS average pain intensity scores after treatment with TENS – either alone or combined with pregabalin – that we observed should therefore be viewed as clinically meaningful. Use of VASs with four different dimensions of pain in PDN was aimed at evaluating which dimensions of pain were relieved more. TENS significantly reduced intensity on three dimensions, namely intensity, unpleasantness and interference with sleep, while interference with daily activities was reduced only in the combined treatment group. The later may not be so clinically important because VAS scores for that dimension were lower in general, which is consistent with patients' observation that pain is worse at night while during work they often forget about it, so it does not have notable influence on daily activities.

The analgesic effects produced by TENS seem to last longer in neuropathic pain than in experimentally induced transient pain.[27] Prolonged efficiency in neuropathic pain was confirmed in our study, since the analgesic effect persisted one month after treatment even though the patients did not receive any pain treatment. That suggests that TENS has durable analgesic effects.

Our results demonstrate some effect of pain treatment on SF-36 scores. TENS and combined treatment treatments had a positive effect on the bodily pain domain of QOL, and to a lesser extent on general health. The observed SF-36 scores also tended to be better in most other domains, though those changes were not statistically significant.

Moderate correlation between pain reduction on VASs and improvements in QOL after treatment with TENS was observed. Reductions on VAS scales correlated

mainly with improvements in vitality, physical functioning and social functioning domains of SF-36, with some correlation also regarding physical role and mental health. This should be seen in the view of previous studies reporting that neuropathic pain has detrimental effects on QOL[27] and the current evidence indicating that pain reduction is not always accompanied by clearly improved quality of life.[28, 29] The lack of very strong associations could be explained by concurrent illnesses, but a more definite interpretation would require a deeper understanding of the quantitative relationship between pain intensity reduction and improvement of QOL then the presently available.

Study Limitations

The most notable limitation is that the trial was not randomized since the randomization protocol was abandoned about half-way into the study because of side-effects associated with pregabalin. Another limitation is the relatively short duration of treatment, particularly in relation to pregabalin, in which maximum benefit of pain relief was not found until eight weeks of treatment although there was an initial plateau of pain relief at four weeks,[22] while in our study the dose was at therapeutic levels only for two weeks, so maximum pain reduction may not have been fully experienced. Finally, because of the initially discussed ethical constraints to the study design, one cannot rule out the possibility that the carry-over benefit one month after treatment merely, or at least partly, reflected the effect of inclusion in a clinical trial, i.e., the placebo effect.

Conclusions

We observed reduced pain associated with improved quality of life in patients with painful diabetic neuropathy treated with TENS to an extent at least equal to what was observed in patients treated with pregabalin or combination of pregabalin and TENS. Despite the limitations of the study, TENS therefore seems to be a viable addition or even alternative to other analgesic modalities, especially because unlike available pharmacological treatments, it has no known side effects. Further trials are recommended to assess TENS efficacy, including long term effects.

References

1. Pirart J. Diabetes mellitus and its degenerative complications: a prospective study of 4400 patients observed between 1947 and 1973. Diabetes Care 1978; 1: 168–88, 252–63.
2. Callisi PT, Jaber LA. Peripheral diabetic neuropathy: current concepts in treatment. Ann Pharmacother 1995; 29: 769–77.
3. Krause S, Backonja M. Development of a neuropathic pain questionnaire. Clin J Pain 2003; 19: 306–14.
4. Dworkin RH, Backonja M, Rowbotham MC, Allen RR, Argoff CR, Bennett GJ, et al. Advances in neuropathic pain: diagnosis, mechanisms and treatment recommendations. Archives of Neurology 2003; 60: 1524–34.
5. Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. Pain 2005; 118: 289–305.
6. Corbett CF. Practical management of patients with painful diabetic neuropathy. Diabetes Educ 2005; 31: 523–40.
7. Jensen MP, Friedman M, Bonzo D, Richards P. The validity of the neuropathic pain scale for assessing diabetic neuropathic pain in a clinical trial. Clin J Pain 2006; 22: 97–103.
8. Fink K, Dooley DJ, Meder WP, Suman-Chauhan N, Duffy S, Clusmann H, et al. Inhibition of neuronal Ca^{2+} influx by gabapentin and pregabalin in the human neocortex. Neuropharmacology 2002; 42: 229–36.
9. Luo ZD, Chaplan SR, Higuera ES, Sorkin LS, Stauderman KA, Williams ME, et al. Upregulation of dorsal root ganglion α_2-δ calcium channel subunit and its correlation with allodynia in spinal nerve – injured rats. J Neurosc 2001; 21: 1868–75.
10. Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms and management. Lancet 1999; 353: 1969–74.
11. Cruccu G, Aziz TZ, Garcia-Larrea L, Hansson P, Jensen TS, Lefaucheur JP, et al. EFNS guidelines on neurostimulation therapy for neuropathic pain. Eur J Neurol 2007; 14: 952–70.
12. Sluka KA, Walsh D. Transcutaneous electrical nerve stimulation: basic science mechanisms and clinical effectiveness. J Pain 2003; 4: 109–21.
13. Melzack R, Wall PD. Pain mechanisms: a new theory. Science 1965; 150: 971–9.
14. De Domenico G. Pain relief with interferential therapy. Aust J Physiother 1982; 28: 14–8.
15. Basbaum AI, Fields HL. Endogenous pain control mechanisms: review and hypothesis. Ann Neurol 1978; 4: 451–62.
16. Feldman EL, Stevens MJ, Thomas PK, Brown MB, Canal N, Greene DA. A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. Diabetes Care 1994; 17: 1281–9.
17. Ware JE, Snow KK, Kosinski M, Gandek B. SF-36 health survey manual and interpretation guide. Boston, MA: The Health Institute, New England Medical Center; 1993.
18. Farrar JT, Young JP, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001; 94: 149–58.
19. Rothman KJ, Michels KB. The continuing unethical use of placebo controls. N Engl J Med 1994; 331: 394–8.
20. Johnson M, Martinson M. Efficacy of electrical nerve stimulation for chronic musculoskeletal pain: a meta-analysis of randomized controlled trials. Pain 2007; 130: 157–65.
21. Dworkin RH, Corbin AE, Young JP Jr, Sharma U, LaMoreaux L, Bockbrader H, et al. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology 2003; 60: 1274–83.
22. Freynhagen R, Strojek K, Griesing T, Whalen E, Balkenohl M. Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. Pain 2005; 115: 254–63.
23. Lesser H, Sharma U, LaMoreaux L, Poole RM. Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial. Neurology 2004; 63: 2104–10.
24. Moore A, McQuay H, Gavaghan D. Deriving dichotomous outcome measures from continuous data in randomized controlled trials of analgesics. Pain 1996; 66: 229–37.
25. Attal N, Cruccu G, Haanpää M, Hansson P, Jensen TS, Nurmikko T, et al. EFNS guidelines on pharmacological treatment of neuropathic pain. Eur J Neurol 2006; 13: 1153–69.
26. Cruccu G, Anand P, Attal N, Garcia-Larrea L, Haanpää M, Jørum E, et al. EFNS guidelines on neuropathic pain assessment. Eur J Neurol 2004; 11: 153–62.
27. Gopalkrishnan P, Sluka KA. Effect of varying frequency, intensity, and pulse duration of transcutaneous electrical nerve stimulation on primary hyperalgesia in inflamed rats. Archives of Physical Medicine and Rehabilitation 2000; 81: 984–90.
28. Deshpande MA, Holden RR, Gilron I. The impact of therapy on quality of life and mood in neuropathic pain: what is the effect of pain reduction? Anesth Analg 2006; 102: 1473–9.
29. Sator-Katzenschlager SM, Schiesser AW, Kozek-Langenecker SA, Benetka G, Langer G, Kress HG. Does pain relief improve pain behaviour and mood in chronic pain patients? Anesth Analg 2003; 97: 791–7.

Arrived 2009-05-21, accepted 2009-07-21