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 dropouts 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 month 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
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 boleč diabetično nevropatijo (PDN), vključno s kakovostjo življenja.

Metode
Načrtovali smo randomiziran klinični poskus z 69 bolnik 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 istopu v raziskavo, po koncu tretodenskega zdravljenja in en mesec po zaključenem zdravljenju.

Rezultati

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. Forty-five percent of patients have pain longer than one year. The presentation and characteristic 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. 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. Available treatment options generally do not provide total relief nor are they effective in all patients. Several pharmacologic symptomatic treatments are available, such as analgesics, antidepressants, anticonvulsants with analgesic profile, dual inhibitor of serotonin and norpinephrine reuptake, serotonin receptor inhibitors, narcotic analgesics, non-steroidal anti-inflammatory drugs and topical therapies. Pregabalin is a selective, high-affinity ligand for the α₂δ subunit of voltage-gated calcium channels, which are thought to play an important role in modulating neuropathic pain. 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. TENS is the application of electrical stimulation of varying frequency, intensity and pulse duration to the skin for pain relief. It is a commonly used nonpharmacologic and non-invasive treatment for pain. Its analgesic mechanisms probably involve gate control theory, physiological block, and endogenous pain inhibitory system. 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) 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. 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 and 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

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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.**

- 69 PDN patients randomised into 3 equal groups without blocking
  - 8 pregabalin
  - 15 combination
  - 9 TENS

- 69 bolnikov s PDN, randomizirani v 3 enake skupine (nebločno)
  - 8 pregabalin
  - 15 kombinacija
  - 9 TENS

- 3 drop-out because of drug side effect
- 1 drop-outs because of accident due to drug side effect
- 37 remaining patients assigned to TENS
- 3 izpadi zaradi stranskih učinkov zdravila
- 1 izpade zaradi nezgod, povezane s str. uč. zdrav.

- 5 PDN patients treated with pregabalin
- 14 PDN patients with combination treatment
- 46 PDN patients treated with TENS
- 5 bolnikov, zdravljenih s pregabalinom
- 14 bolnikov, zdravljenih kombinirano
- 46 bolnikov, zdravljenih s TENS

- skupini s pregabalinom in komb. ustavljeni
- preostalim bolnikom dodeljen TENS

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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). 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 ($\rho$) 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
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 \(\approx 0.005\), 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.
No difference was found between groups regarding relative change either in VAS scores or in SF-36 domains. 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 statistically significant differences from Wilcoxon tests with Bonferroni correction; NS = not significant; NA = not applicable. DA = daily activities.
Table 3. Descriptive statistics and results of statistical tests for SF-36 scores.

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

<table>
<thead>
<tr>
<th>SF-36 domain</th>
<th>Baseline</th>
<th>At the end of treatment</th>
<th>One month post treatment</th>
<th>Relative raise from baseline to end of treatment</th>
<th>Comparison between time-points</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36 domain</td>
<td>Zacetek</td>
<td>Konec zdravljenja</td>
<td>Mesece dni po koncu zdravljenja</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TENS TENS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PF – Physical funct. / PF – telesno delovanje</td>
<td>65 (50, 81)</td>
<td>68 (45, 90)</td>
<td>78 (54, 85)</td>
<td>0% (~15%,13%)</td>
<td>NS</td>
</tr>
<tr>
<td>RP – Physical role / RP – telesna vloga</td>
<td>75 (10, 100)</td>
<td>88 (19, 100)</td>
<td>75 (25, 100)</td>
<td>0% (~0%,33%)</td>
<td>NS</td>
</tr>
<tr>
<td>RE – Emotional role / RE – ľustvena vloga</td>
<td>100 (35, 100)</td>
<td>100 (35, 100)</td>
<td>100 (35, 100)</td>
<td>0% (~0%,12%)</td>
<td>NS</td>
</tr>
<tr>
<td>BP – Bodily pain / BP – telesna bolečina</td>
<td>41 (31, 61)</td>
<td>61 (41, 74)</td>
<td>62 (41, 74)</td>
<td>24% (~0%,51%)</td>
<td>NS</td>
</tr>
<tr>
<td>VI – Vitality / VI – vitalnost</td>
<td>55 (60, 61)</td>
<td>58 (44, 71)</td>
<td>58 (40, 75)</td>
<td>0% (~18%,33%)</td>
<td>NS</td>
</tr>
<tr>
<td>MH – Mental health / MH – duševno zdravljenje</td>
<td>68 (56, 80)</td>
<td>68 (56, 80)</td>
<td>70 (52, 84)</td>
<td>0% (~13%,14%)</td>
<td>NS</td>
</tr>
<tr>
<td>SF – Social funct. / SF – socialno delovanje</td>
<td>75 (59, 91)</td>
<td>75 (50, 100)</td>
<td>75 (63, 88)</td>
<td>0% (~19%,20%)</td>
<td>NS</td>
</tr>
<tr>
<td>GH – General health / GH – splošno zdravljenje</td>
<td>59 (29, 62)</td>
<td>41 (29, 65)</td>
<td>49 (35, 62)</td>
<td>0% (~12%,25%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

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 significant differences from Wilcoxon tests with Bonferroni correction; NS = not significant; NA = not applicable.

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 celotno vzorec).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Zdravljenje</th>
<th>TENS TENS (N = 46)</th>
<th>Pregabalin (N = 5)</th>
<th>Combined Kombinirano (N = 14)</th>
<th>Unadjusted Nepopravi</th>
<th>p</th>
<th>Total sample Celotni vzorec (N = 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average pain / Povprečna bolečina</td>
<td>Intensity / Jakost</td>
<td>26</td>
<td>3</td>
<td>7</td>
<td>0.917</td>
<td>36 (55%)</td>
<td>NS</td>
</tr>
<tr>
<td>Unpleasantness / Neprijetnost</td>
<td>26</td>
<td>5</td>
<td>5</td>
<td>0.950</td>
<td>34 (52%)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Interference with DA / Motenje DA</td>
<td>20</td>
<td>1</td>
<td>5</td>
<td>0.654</td>
<td>26 (40%)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Interference with sleep / Motenje spanja</td>
<td>23</td>
<td>4</td>
<td>7</td>
<td>0.502</td>
<td>34 (52%)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Worst pain / Najhujša bolečina</td>
<td>Intensity / Jakost</td>
<td>13</td>
<td>0</td>
<td>4</td>
<td>0.539</td>
<td>17 (26%)</td>
<td>NS</td>
</tr>
<tr>
<td>Unpleasantness / Neprijetnost</td>
<td>16</td>
<td>1</td>
<td>5</td>
<td>0.605</td>
<td>20 (31%)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Interference with DA / Motenje DA</td>
<td>12</td>
<td>2</td>
<td>6</td>
<td>0.495</td>
<td>20 (31%)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Interference with sleep / Motenje spanja</td>
<td>20</td>
<td>3</td>
<td>5</td>
<td>0.840</td>
<td>29 (45%)</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

Average pain / Povprečna bolečina:
- Intensity / Jakost
  - TENS TENS: 26
  - Pregabalin: 3
  - Combined: 7
  - Unadjusted: 0.917

Worst pain / Najhujša bolečina:
- Intensity / Jakost
  - TENS TENS: 13
  - Pregabalin: 0
  - Combined: 4
  - Unadjusted: 0.539

Table 3. Description of results and statistical results for SF-36 scores. Table 4. Share of patients with at least 30% improvement in outcome measures (comparison between groups and estimate for the total sample).
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. In such situations, one solution is to use an existing drug for the same disease as an active comparator in an equivalence trial. 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.

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, whereby the last week is wash-out period. That suggests that TENS has durable analgesic effect.

Prolonged efficiency in neuropathic pain was confirmed in our study, since the analgesic effect persisted one month after treatment. 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.

The analgesic effects produced by TENS seem to last longer in neuropathic pain than in experimentally induced transient pain. 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 VAS 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, and the current evidence indicating that pain reduction is not always accompanied by clearly improved quality of life. 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, 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