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TENS – an alternative to antiviral drugs for acute herpes zoster treatment and postherpetic neuralgia prevention

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Summary

QUESTIONS UNDER STUDY: To evaluate the effectiveness of transcutaneous electrical nerve stimulation (TENS) in treatment of Herpes zoster (HZ), and prevention of postherpetic neuralgia (PHN) compared with antiviral drugs. PHN is frequent complication of HZ and may last for months, its treatment isn't very successful. Nonpharmacological regimens for treatment of HZ and prevention of PHN haven't been evaluated.

METHODS: Retrospective observational study of medical records of patients of three family physicians in Health centre Litija, Slovenia was done. 109 of 6613 patients on their lists had HZ from 1999 to 2008. 102 medical records were analyzed (6 could not be reached; one patient with corneal HZ was excluded).

RESULTS: Four treatment groups were compared: only TENS therapy, only antiviral drug, antiviral drug and TENS, no therapy (neither antiviral drug or TENS). All groups were similar with respect to demographic characteristics of patients with HZ. Patients treated only with TENS had no PHN, 28.6% of patients treated with antiviral drugs had PHN. Less analgesic drugs have been prescribed to patients treated only with TENS.

CONCLUSION: Study suggests TENS may be safe adjunct or even alternative to antiviral drugs for treatment of acute HZ. It looks that TENS may be at least as good as antiviral drugs for treatment of HZ, and it may be better in reducing and preventing PHN – such conclusion would necessitate controlled, prospective study. Use of TENS provided pain relief and resolution of skin lesions with no higher rate of other HZ complications compared to antiviral therapy.

Key words: *Herpes zoster; TENS; prevention; postherpetic neuralgia*

Introduction

Herpes zoster (shingles) is a commonly encountered disorder in general practice. It is caused by reactivation of the human herpes virus type 3 (varicella zoster virus) which becomes latent in the dorsal root sensory ganglia after primary infection (clinically manifested as varicella). If it becomes active again, it spreads to the corresponding dermatome, and generate the characteristic unilateral vesicular exanthema. The accompanying inflammation of the sensory nerve and skin damage are supposedly responsible for the associated significant acute pain. Prodromal symptoms, burning pain, itching, and malaise precedes the rash for several days and are common [1, 2].

The reported incidence varies from 1.2/1000 to 11.8/1000 people per year, with age the incidence is increasing; the incidence in people aged over 80 is about 10/1000/year [1, 3–6]. Most immunocompetent patients will experience spontaneous and complete recovery within a few weeks, but some will develop complications, and the most common is postherpetic neuralgia in the affected dermatome.

Postherpetic neuralgia (PHN) is the condition if the pain persists more than one month (some authors suggest more than 3 months and some even more than 6 months) after the rash has resolved [1, 7–9]. Predictors of PHN are: greater age, acute pain and rash severity, prodromal pain, the presence of virus in peripheral blood as well as adverse psychosocial factors [1, 7]. The reported incidence of PHN is age dependent: the risk is low (2%) in patients younger than 50 years of age, 20% in those older than 50 years and 35% in those over the age of 80 years [9–12]. More than 5% of elderly patients have PHN at 1 year after acute HZ [7, 11].

Herpes zoster (HZ) is usually treated with orally administered antiviral drug (acyclovir, famcyclovir, valcyclovir, brivudin). The antiviral medications are most effective when started within 72 hours after the onset of the rash [1, 13, 14].

Therapy for acute HZ is intended to reduce acute pain, hasten rash healing, and reduce the risk of PHN and other rare complications. Antiviral drugs could be close to achieving these aims, but meta-analyses have shown no or only a partial effect on the incidence of PHN [1, 11, 15, 16]. Nerve blocks and tricyclic antidepressants may reduce the risk of PHN although firm evidence is lacking; topical lidocain patches frequently reduce allodynia [1, 7].

Current evidence supports that multiple medications are effective in reducing the PHN (but not for reducing the incidence of PHN): tryciclic antidepressants, antiepileptics, opioids, NMDA receptors antagonists as well as topical lidocain and capsaicin; sympathetic blockade may assist in treating the pain of herpes zoster or PHN; transcutaneous electrical nerve stimulation (TENS) or percutaneous electrical nerve stimulation (PENS) may be effective in some cases [1, 7, 14, 17–21]. The newly released vaccine against HZ may lead to reductions in HZ and PHN morbidity [1, 3, 22], but this is not sure because the vaccination is not wide-spread and the proportion of old people in next decades will increase and HZ is more frequent in elderly.

Only few studies have been published on HZ treatment without antiviral drugs treatment although some studies showed that alternative treatment regimens as TENS or PENS seemed very good in resolving the rash, decreasing the herpes-related pain and even effective in preventing PHN [17, 23–25].

The aims of this study was to find out the effectiveness of TENS in treating HZ and in preventing PHN in comparison with a standard antiviral drugs regimen among patients of three family physicians (FP) in the Health centre Litija, Slovenia.

Methods

A retrospective observational study of paper-based and electronic patients' medical records and data in three FP practices of the Health centre Litija, Slovenia (that used different approaches to the treatment of acute HZ) was done. At the beginning electronic data were analysed to identify all the patients who had had HZ since the year 1999 till the end of 2008. Then paper-based and electronic medical records of all these patients were reviewed to get data on the course and treatment of HZ, data on eventual PHN, and its course.

There were 6613 patients on FPs' lists during this period and 109 of them had HZ. Six medical records could not be reached because these patients have moved away during these years, and 1 patient with corneal HZ has been excluded because he had been treated at hospital. The diagnosis of HZ was made by clinical examination on the basis of typical unilateral vesicular exanthema.

One group of patients received only TENS therapy – all these patients were on the list of one FP (an older FP that has been treating HZ always only with TENS since late 80's). The second group received only antiviral drug (aciclovir 800 mg five times a day for 1 week or famciclovir 1000 mg three times a day for 1 week) – these patients were mostly on the list of another FP. The third group received antiviral drug at the same regimen together with TENS therapy – these patients were mostly on the list of the third FP. In the fourth group patients of all three FPs were included: antiviral drug/TENS therapy started more than 72 hours after the rash had appear or they received no therapy – neither antiviral drug, neither TENS therapy (they received only topical or analgetic therapy because they came to their doctors more than 72 hours after the rash had appear). The TENS therapy for the treatment of acute HZ consisted of the placement of two patches on the skin at the dermatome infected: one patch placed at paravertebral region, another patch on the other side along the nerve for 30 minutes five times a week for 2 or 3 weeks. The patches were connected to a low output (1–5 mA) electrical generator and stimulated at frequences ranging from 20 to 40 Hz. The majority of patients received analgetic oral drugs (paracetamol, nonsteroid antirheumatic drug or tramadol). Some patients received also a topical treatment (Rp. Pastae zynci).

At the end the collected data were analyzed by SPSS 16.0 for Windows.

This retrospective study has been approaved by the National Medical Ethics Committee on March 18th, 2008, No. 81/03/08.

Results

Data for 102 patients were analyzed. The incidence of HZ in analyzed three FPs' patient population was 1.8/1000. Much more women experienced HZ infection, but there was no sex difference in frequency of PHN. The average age of patients was almost 70 years, 13.7% of them were younger than 50 years. More than half of patients had rash on thoracic region. Only 7.5% of patients under 70 years had PHN, but 21.3% patients aged 70 years or more had PHN.

Each of four groups of patients (described in Methods section) had between 21 to 29 patients. These four treatment groups were similar with respect to demographic characteristics of patients with acute HZ and to the severity of rash (number of skin lesions) – table 1. A little more patients (not significant: Chi square test – P = 0.066) with the rash localized at their heads and/or neck were treated with antiviral drugs. Among patients that received no therapy were a little more patients younger than 50 years (not significant: Chi square test – P = 0.172) and a little more males (not significant: Chi square test – P = 0.886).

There were differences in receiving different treatment of HZ and the age of patients (Chi square test – P = 0.001). 12 of 29 (41.3%) patients aged 80 years or more were treated only with TENS, 2 of 28 (7.6%) only with antiviral drugs and 13 of 24 (54,1%) with both. Localisation of rash was not related to the frequency of PHN (Chi square test: P = 0.682).

There were significant differencies in patients' experiences of pain during acute HZ in different treatment groups (Chi square test: P = 0.024) – table 2. The severity of pain has not been documented in patients' records quantitatively (e.g., by VAS – visual analogue pain scale), here is only an assumption according to doctors' notes in patients' medical records and prescribed analgesic drug. Patients treated with TENS received less nonsteroid anti-inflammatory drugs or/and tramadol than patients in groups treated only with antivirotic drugs or with no therapy.

16.2% of patients with HZ had PHN, mostly older than 70 years; only three patients with PHN were younger than 70 years. There was a significant difference in experiencing PHN among patients with different treatment regimen (Chi square test: P = 0.024) – (table 3). Patients treated with TENS have no PHN; patients treated with antiviral drugs had the highest proportion of PHN (28.6%). There was no

other complication found among patients in this study except three patients with secondary bacterial inflamation of skin lesions – two in group treated with antiviral drug and one in group treated with TENS.

Discussion

This retrospective study suggests that TENS may be a godd adjunct or even viable alternative to antiviral drugs for the treatment of acute HZ. It looks that TENS may be at least as good as antiviral drugs in treatment of HZ, but it looks it may be much better in reducing PHN, actually TENS may even prevent PHN. The use of TENS provided also pain relief, resolution of skin lesions with no higher rate of other possible complications of HZ compared to standard antiviral therapy. TENS has also another advantage: there is almost no contraindications for its use except implanted pacemaker and malignant skin lessions, its use has no harmful side effects.

The incidence of HZ in patients' population in our study was similar to the incidence reported in many studies in other countries [1, 26, 27], but a little lower than in national epidemiologic study in our country, 1.8/100000 versus 3.2/100000 [6]. The incidence of PHN (16.2%) also was similar to other published data as well as the frequency distribution of PHN related to age [10, 14, 23]. We found similar difference in incidence of HZ by sex (it is more frequent at women) as it was reported in other studies [4, 14]. Age distribution of patients with acute HZ and the thoracic region as most frequent localisation of rash, were also similar to data from other studies [4, 23, 27].

The good point of this study was that there's was no important difference in demographic characteristics of patients receiving different therapeutic procedures; the only difference was that more patients aged 80 years or more were treated only with TENS. One may presume that older patients may appear more ill or may be more imunocompromised, but anyway this group of patients experienced no PHN, although the incidence of PHN usually is higher at older patients [9–12]. There was also no important difference in severity of rash measured by the number of skin lesions, so the comparison was more reliable.

Patients' inclusion in different treatment groups can hardly be considered as biased because each of three FPs decided to treat all his patients with the same treatment regimen – they performed no selection. The only difference was at patients that came more than 72 hours after the rash had appeared: without any systematic selection some of them received no treatment, but some of them received the same treatment as if they would come in time; FPs decisions were propably made according to patients' wishes.

The most interesting result of our study was that no patient who received only TENS therapy had PHN, but on the other hand more than 20% of patients that received antiviral drugs had PHN. So it looks that early treatment of HZ with TENS may be better in preventing PHN – such con-

Table 1: Demographic characteristics of patients with acute Herpes zoster receiving TENS* or antiviral drug alone or antiviral drug with TENS or no therapy.

	Antiviral drug	Antiviral drug with TENS	TENS	No therapy	Total	P value
Patients (n)	28	24	29	21	102	
Male / female (%)	25.0/75.0	25.0/75.0	24.1/75.9	33.3/66.6	26.5/ 73.5	0.886 NS†
Age (years), mean ± SD	63.8 ± 14.1	76.9 ± 14.5	74.0 ± 16.6	59.6 ± 16.0	68.9 ± 16.6	
≤50 years (%)	10.7	8.3	10.3	28.6	13.7	
≥51 years (%)	89.3	91.7	89.7	71.4	86.3	0.172 NS
Location of rash (%)						0.066 NS
Thorax	46.4	37.5	55.2	71.4	52.0	
Head and/or neck	28.6	29.2	6.9	14.3	19.6	
Lumbar and abdomen	7.1	4.2	17.2	14.3	10.8	
Extremities	17.9	29.1	20.7	0.0	17.6	

**TENS = transcutaneus electrical nerve stimulation*
†*NS = not significant (Chi square test*: P *>0.05)*

Table 2: Pain severity during acute herpes zoster in differently treated groups of patients.

Severity of pain‡	TENS	Antiviral drug	Antiviral drug with TENS	No therapy	Total
Mild	9	8	9	2	28
Moderate	8	1	5	2	16
Intense	12	19	10	17	58
Total	29	28	24	21	102

‡*Pain severity was defined according to the prescribed analgesic drug: mild = prescribed no analgesics, moderate = prescribed only paracetamol, intense = prescribed nonsteroid anti-inflammatory drug or/and tramadol*

Table 3: Effect of different treatment regimen (antiviral drug or TENS* therapy or both or no therapy) on the incidence of PHN§.

Number of patients with PHN	TENS *Number (%)*	Antiviral drug *Number (%)*	Antiviral drug with TENS *Number (%)*	No therapy *Number (%)*
Without PHN (%)	29 (100.0)	20 (71.4)	19 (79.2)	18 (85.7)
PHN <6 months (%)	0 (0.0)	8 (28.6)	5 (20.8)	3 (14.3)
PHN >6 months (%)	0 (0.0)	3 (10.7)	4 (16.7)	2 (9.5)

**TENS = trancutaneus electrical neurostimulation*
§*PHN = postherpetic neuralgia (persistent neuralgia one month after the rash has resolved)*

clusion –would certainly necessitate a controlled, prospective study. The combination of treatment with TENS and antiviral drugs did not prevent PHN no better than antiviral drugs alone, although one could expect at least the same or even better preventive effect of such combination. Data of our study give no clear explanation for this, neither explanation can be found in the published literature because there is no study on simultaneous use of TENS and antiviral drugs in acute HZ. One hypothesis could be that antiviral drugs reduce the effect of TENS, or/and that simultaneous use of antiviral drugs and TENS doesn't have favorable effect on PHN. Lower rate of PHN in the fourth group of patients with no therapy/too late therapy could be explained with TENS treatment which some of them received. A randomized prospective study with much greater number of patients, that would compare patients with different regimens of treatment (these four regimens), can clarify this and maybe give an explanation, and also corroborate the findings of our research. Such study probably could not be double blinded because it is not possible to mimic persuasively the sensation provided by the electrical stimulation by TENS (but the outcome assessment could be blinded to the assessing researcher). Such study could also give an answer to the cost – benefit question. If TENS therapy in controlled prospective studies would show as good effect as antiviral drugs therapy in treament of acute HZ and maybe even more effective in reducing PHN, then such therapy is also cheaper considering high costs of antiviral drugs and all the different treaments of PHN that usually last several months [9, 29].

An important observation of this study was that among all patients there was no serious complications in any treatment group although there were also some imunocompromised patients which are at higher risk for complications. But, we have to stress that the patient with ophthalmic HZ was not included in the analysis.

This retrospective study can be criticized because of relatively small number of patients in all four groups. It is true that greater sample would be better and more convincing. Our limitation was the number of all patients in these three practices where we can expect 12 to 20 patients with HZ per year [27].

Our assumption on the severity of pain could be criticized because we relied only on doctors' notes in patients' medical records and on the prescribed analgetic medicine. It certainly would be better if patients' pain had been measured by VAS scale. This was not possible because this study was retrospective, and it had not been planned ten years ago when several important factors could be defined and organized to be followed sistematicly. So, our findings may have some limitations. As we found that more patients that received antiviral drug received more potent analgetic drugs (compared to patients at TENS treatment) one may put different hypothesis: **1)** TENS therapy is more effective in reducing pain in acute HZ, **2)** patients with more severe HZ were treated with antiviral drugs (and so they needed more analgetics), **3)** doctors' scepticism about effect of antiviral drugs on pain.

Another limitation of our study was that reviewing medical records it was not possible to find out exact course of acute HZ (e.g., the course of skin lesions from vesicles to crusting and to healing in days, the exact course of acute pain, its influence on daily activities, and quality of sleep) because the study had not been planned at the beginning, and so the notes in patients' medical records were not "standardized" which is a typical weakness of retrospective observations. But, according to medical records' data it can be hypothesized that the resolution of rash and pain relief at patients with TENS therapy was at least as fast as (or even faster) at other patients because they needed less analgesic drugs.

One more weak point could be that the severity of exanthema of each patient could not be defined from notes in patients' medical records. One could hypothesize that TENS had been used only in patients with a weak exanthema and this might bias the probability of the development of PHN. But, it could hardly be biased because the treatment group which received only TENS therapy were patients of one FP and it is not likely that all his patients would be with a weak exanthema.

In conclusion, in this study TENS therapy seems to be an adjunct to the standard HZ therapy or maybe even an effective, safe, harmless, and cheap approach to treating patients with acute HZ and reducing the frequency of PHN that compared favorably with standard antiviral drug therapy. It looks that it not only reduces but may even prevent PHN with no higher rate of other complications of HZ compared to standard antiviral therapy. Anyway, data of this retrospective study should be interpreted with caution because of the mentioned weak points and the definite answer for drawing such conclusions would necessitate a controlled, prospective study. Such treatment may be of special interest for multimorbid patients that are already taking several different drugs and another drug could be the problem because of drug interactions and also patients' adherence [30].

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