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ORIGINAL ARTICLE

Transcutaneous electrical nerve stimulation for reduction of pruritus in macular amyloidosis and lichen simplex

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ABSTRACT

Lichen simplex (LS) is characterized by circumscribed, lichenified, pruritic patches that may develop on any part of the body. Macular amyloidosis (MA) is the form of primary localized cutaneous amyloidosis. Transcutaneous electrical nerve stimulation (TENS) uses a pulsed electric current generated transcutaneously by a device to cause impulses to be carried along large-diameter afferent nerves. In this article, we report the effects of TENS on the Dermatology Life Quality Index (DLQI) measures and visual analogue scale (VAS) scores in patients with pruritus, in whom LS and MA were diagnosed. All patients with MA and six (75%) patients with LS had relief of their pruritus with TENS therapy. At week 2, there was a significant difference in median VAS scores between baseline in the group of LS ($P = 0.007$). At 4 weeks of therapy, statistically significant differences were observed compared with the baseline and week 2 in the median VAS scores in the group of MA ($P < 0.001$). There was also a statistically significant improvement in median DLQI total scores with respect to baseline, which was achieved as early as week 2 in patients with LS and MA who were on the TENS treatment ($P = 0.006$, $P = 0.001$, respectively).

Key words: Dermatology Life Quality Index, lichen simplex, macular amyloidosis, pruritus, transcutaneous electrical nerve stimulation, visual analogue scale.

INTRODUCTION

Lichen simplex (LS) is characterized by circumscribed, lichenified, pruritic patches that may develop on any part of the body. The underlying stimulus for the development of LS is pruritus. Various topical treatments, including potent topical corticosteroids, doxepin cream, capsaicin cream and intralesional corticosteroids are used for the therapy of LS. In most patients, however, they do not permanently abolish the itchiness.[1–5]

Macular amyloidosis (MA) is the secondmost common form of primary localized cutaneous amyloidosis. MA usually presents as pruritic, brownish macules that coalesce to form symmetric patches with a characteristic rippled or reticulated pattern involving most frequently the upper back. The diagnosis can be based on its clinical characteristic appearance and on the skin biopsy findings. It is generally accepted that amyloid material occurs mainly as a result of keratinocyte degeneration and there is no relation with systemic amyloidosis. It is not known whether pruritus develops first and leads to damage of keratinocytes or whether pruritus is secondary to deposition of amyloid. The treatment options of MA such as topical corticosteroids,

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calcipotriol, 0.1% tacrolimus, dimethylsulfoxide, ultraviolet (UV) B and oral acitretin have been tried with highly variable results. There is so far no established mode of curative treatment for MA.[6–13]

Based on these findings, treatment that rapidly alleviates pruritus could be considered a major goal in the management of LS and MA.

Transcutaneous electrical nerve stimulation (TENS), which uses a pulsed electric current generated transcutaneously by a device, probably causes impulses to be carried along large-diameter afferent nerves. Subsequently, it is thought to produce presynaptic inhibition of nociceptive A delta and C fibers involved in the pain gates in the substantia gelatinosa and thus have an effect in pain control. No definitive pathway for itching has been shown, but it is thought that TENS may work in a similar way in its effect on pain.[1,14–19]

During the past decade, the Dermatology Life Quality Index (DLQI) has been used in a number of studies of dermatological diseases including generalized pruritus, eczema, psoriasis and others to evaluate the impact of disease and its treatment on the lives of these patient populations. [20–24]

In this article, we report the efficacy of TENS on the DLQI measures and visual analog scale (VAS) scores in pruritus of patients in whom LS and MA were diagnosed.

METHODS

The clinical study protocol was approved by the Gaziosmanpaşa University Hospital Local Ethics Committee. The study was conducted from August 2009 to March 2010 in accordance with the Declaration of Helsinki principles. Written informed consent was obtained from each patient in the study prior to intervention.

Patients

A total of 16 patients were enrolled. Eight patients (five women and three men) had a diagnosis of LS and the remaining eight patients (all of them were women) had a diagnosis of MA. The median and interquartile range (IQR) values of patient ages with diagnosis of LS and MA were 39.0 (IQR 15) and 39.5 (IQR 23) years, and the disease durations were 3.5 (IQR 9) and 5.5 (IQR 7) years, respectively. Patient characteristics are shown in Table 1. Inclusion criteria were as follows; a history of intermittent attacks of itching localized area, age above 18 years, presence of at least one localized lichenified plaque of LS and one localized dark patch of MA on the following sites: neck, back, arm or leg for a period of at least 1 year, which did not respond to topical treatment with corticosteroids, moisturizers and systemic antihistamines. The diagnosis of LS was made with clinical examination and lesions secondary to predisposing skin disorder were excluded. The clinical diagnosis of MA was confirmed by histopathologic examination of punch biopsy material stained by hematoxylin-eosin, Congo red and crystal violet. The duration and localization of the disease and previous treatments were recorded. All cases were evaluated with regard to other dermatoses (such as atopic eczema) and/or systemic diseases that might cause local or systemic pruritus. This screening was carried out by a detailed physical and dermatologic examination and laboratory tests, including a routine biochemistry panel, complete blood count, thyroid function tests, serum total immunoglobulin E (Ig E), urine analysis, stool examination for parasites and chest X-ray radiographic examination. Exclusion criteria included cardiovascular diseases including cardiac pacemaker insertion and loss of sensation at the treatment site. All patients abstained from using any systemic treatment, including antihistamines and topical corticosteroids 2 weeks before the treatment. Cases were allowed to apply moisturizers during the therapy.

Table 1. Baseline characteristics of patients

	Total (n = 16)	Lichen simplex (n = 8)	Macular amyloidosis (n = 8)	P-value
Age, year†	39 (15)	39.0 (15)	39.5 (23)	0.916
Disease duration, year†	5 (9)	3.5 (9)	5.5 (7)	0.454
Gender, n (%)				
Female	13 (81.2)	5 (62.5)	8 (100.0)	0.200
Male	3 (18.8)	3 (37.5)	0 (0)	
Location, n (%)				
Back	9 (56.3)	4 (50.0)	5 (62.5)	0.250
Leg	2 (12.5)	2 (25.0)	0 (0)	
Neck	4 (25.0)	1 (12.5)	3 (37.5)	
Arm	1 (6.2)	1 (12.5)	0 (0)	

†Values are presented as median and interquartile range (IQR).

Transcutaneous electrical nerve stimulation

All patients received conventional TENS to the pruritic areas with most intense itching defined by them. High-frequency (50–100 Hz) TENS applications of 30 min duration with a pulse width 40–75 μs were given from a dual-channel portable TENS unit (BioMed Plus TENS Machine, Biomedical Life Systems Inc., Vista, CA, USA) with four 4 × 5 cm surface carbon electrodes. These were applied using a gel-based coupling agent for the transmission of electrical impulses. The intensity of TENS was adjusted until the patient reported tingling sensation in their muscles. The treatment was given thrice weekly, for 4 weeks with a total of 12 sessions at the end of the period. The patients were carefully examined at each visit to evaluate any side-effects such as erythema, swelling, irritation or numbness.

Measures

Visual analog scale

The itching scale used in this study was used to measure the severity of itching, at week 0, 2 and 4 (at the end of the study) using a horizontal VAS. The scale ranged from 0 (no itching) to 10 (severe itching). All assessments were made by the same clinician.

Dermatology life quality index

The DLQI was developed for use in a dermatology clinical setting, to assess limitations related to the impact of skin disease and its treatment. It consists of 10 items and six domains including: symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment. Response categories include ''not at all'', ''a little'', ''a lot'', and ''very much'' with corresponding scores of 0, 1, 2 and 3 respectively; the response ''not relevant'' (and unanswered items) are scored as ''0''. A total score is calculated by summing the score of all items, resulting in a maximum score of 30 and a minimum score of 0. Scale scores are calculated for each domain. The DLQI has well-established reliability and validity when used in generalized pruritus, atopic eczema, psoriasis and others.[20–24] The assessments of DLQI in all patients were performed at week 0, 2, and 4 (at the end of the study) by another clinician.

Patient-reported treatment assessment score

All patients were asked to rate the assessment score of their treatment on a six-point scale (−1 = worsening of itch, 0 = no change, 1 = mild reduction of itch, 2 = moderate reduction of itch, 3 = marked reduction of itch, 4 = no itch) at the end of the study (at week 4).

Patient-reported recurrence score of itch

Patients were also asked to rate the recurrence score of itch on a four-point scale (0 = no recurrence, 1 = mild itch, 2 = moderate itch, 3 = severe itch) after 2 months of the study.

Statistical analysis

Fisher's exact χ^2 tests were used to compare the categorical variables among groups. Categorical variables were presented as count and percentages. Mann–Whitney *U*-test was used to compare the scales between the two groups. Friedman analysis of variances were carried out to compare the scales between the two groups. When Friedman analysis of variances results were significant, Bonferroni-adjusted Wilcoxon signed-rank test was conducted for pairwise comparisons. Continuous variables were presented as median and interquartile range (IQR). Two-tailed *P*-values <0.05 were considered as statistically significant. Analyses were performed using commercially available software (PASW ver. 18, ID: 33478001 SPSS inc. Chicago, IL, USA).

RESULTS

All of the cases completed the treatment and returned for follow up. No side effects were observed or reported by the patients except for a mild local erythema in one patient with diagnosis of LS, which did not require withdrawal of therapy.

The effects of TENS treatment are summarized in Table 2. All of the patients with MA and six (75%) patients with LS had relief of their pruritus with TENS therapy. At week 2, there was a significant difference in median VAS scores between baseline in the group of LS ($P = 0.007$), (Fig. 1). At 4 weeks of therapy, statistically significant differences were observed compared with the baseline and the week 2 in median VAS scores in the group of MA ($P < 0.001$), (Fig. 1). There was also a statistically significant improvement

Table 2. Outcomes of transcutaneous electrical nerve stimulation (TENS) treatment in pruritus of lichen simplex and macular amyloidosis

Scores	Treatment	Total (n = 16)	Lichen Simplex (n = 8)	Macular Amyloidosis (n = 8)	P**
VAS	Baseline	8 (4)	8 (4)	8 (4)	0.340
	Week 2	4 (0)	4 (0)	4 (0)	0.644
	Week 4	2 (4)	3 (6)	2 (2)	0.442
	P***	<0.001†	0.007‡	<0.001†	
DLQI symptoms and feelings	Baseline	4 (2)	4 (3)	3.5 (1)	0.479
	Week 2	2 (0)	2 (2)	2 (0)	0.700
	Week 4	2 (2)	2 (4)	1.5 (2)	0.577
	P***	<0.001§	0.006‡	0.001§	
DLQI daily activities	Baseline	2 (3)	3 (4)	2 (3)	1.000
	Week 2	1 (2)	0.5 (2)	1 (2)	0.578
	Week 4	0 (2)	0 (2)	0 (0)	0.239
	P***	<0.001§	0.015¶	0.002¶	
DLQI leisure	Baseline	2 (4)	1.5 (4)	2 (4)	0.956
	Week 2	0 (2)	0 (2)	0 (2)	0.699
	Week 4	0 (0)	0 (2)	0 (0)	0.535
	P***	<0.001§	0.032‡	0.010¶	
DLQI work and school	Baseline	1 (2)	1 (2)	1 (2)	0.783
	Week 2	0 (1)	0 (1)	0 (1)	0.747
	Week 4	0 (1)	0 (1)	0 (0)	0.239
	P***	0.001§	0.061	0.006¶	
DLQI treatment	Baseline	0 (0)	0 (0)	0 (0)	1.000
	Week 2	0 (0)	0 (0)	0 (0)	
	Week 4	0 (0)	0 (0)	0 (0)	
	P***	1.000	1.000	1.000	
DLQI personal relationship	Baseline	2 (2)	4 (2)	2 (2)	0.088
	Week 2	2 (2)	2 (2.75)	1.5 (2)	0.463
	Week 4	0 (2)	1 (2)	0 (2)	0.268
	P***	<0.001§	0.010¶	0.018¶	
DLQI total	Baseline	12.5 (8.25)	13 (8)	10.5 (8.25)	0.493
	Week 2	4.5 (6)	4.5 (9)	4.5 (4)	0.916
	Week 4	2 (8)	3 (11)	1.5 (3)	0.520
	P***	<0.001§	0.006‡	0.001§	
Therapy assessment		3 (3)	2.5 (4)	3 (1)	0.510
Recurrence		0 (1)	0.50 (3)	0 (1)	0.182

Values are presented as median and interquartile range (IQR). **Two-tailed P-values from Mann–Whitney U-test assessments for between the groups of lichen simplex and macular amyloidosis. ***Two-tailed P-values from Friedman analysis of variance assessments for among baseline, week 2 and week 4 treatment. Multiple comparison test (Wilcoxon signed rank test with Bonferroni adjustment) results: ‡There was statistically significant difference between baseline and week 4 treatment ($P < 0.05$) but no statistically significant difference between week 2 and others ($P > 0.05$). ‡There was statistically significant difference between baseline and other weeks ($P < 0.05$) but no statistically significant difference between week 2 and week 4 ($P > 0.05$). §There was statistically significant difference between baseline and week 2 treatment ($P < 0.05$) but no statistically significant difference between week 4 and others ($P > 0.05$). ¶There was statistically significant difference between all pairwise comparisons. DLQI, Dermatology Life Quality Index.

in median DLQI total scores with respect to baseline, which was achieved as early as at week 2 in patients with LS and MA who were on the TENS treatment ($P = 0.006$, $P = 0.001$, respectively), (Fig. 2). The improvement in DLQI total scores were maintained at week 4 in the group of MA ($P = 0.001$) but the group of LS showed nonsignificant improvement during this period ($P > 0.05$), (Fig. 2). In addition, significant differences in median scores for all of the DLQI subscales except in DLQI treatment were found from baseline to week 4 in patients with MA (all $P \leq 0.018$). The patients with LS showed significant improvement in median scores in DLQI symptoms and feelings and leisure from baseline to week 2 ($P = 0.006$, $P = 0.032$, respectively), and in DLQI daily activities and personal relationships from baseline to week 4 ($P = 0.015$, $P = 0.010$, respectively). At 4 weeks of therapy, the median treatment

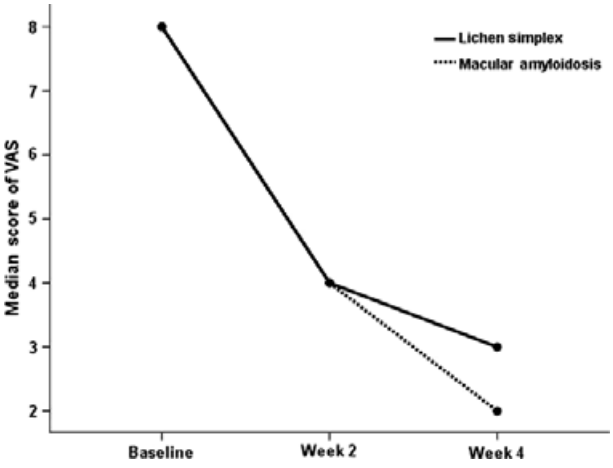

Figure 1. Weekly changes of median score of visual analog scale (VAS) for lichen simplex and macular amyloidosis by the treatment of transcutaneous electrical nerve stimulation (TENS).

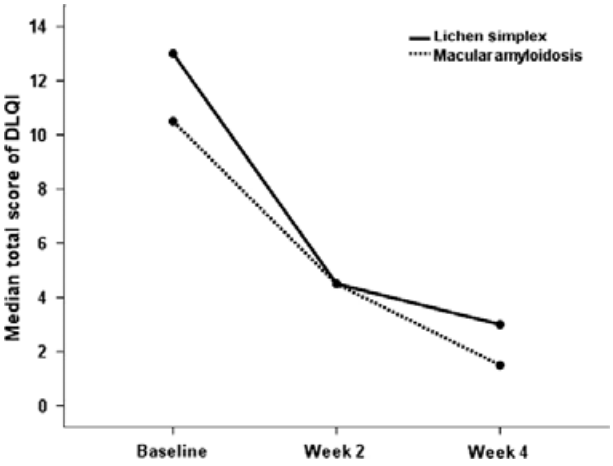

Figure 2. Weekly changes of median total score of Dermatology Life Quality Index (DLQI) for lichen simplex and macular amyloidosis by the treatment of transcutaneous electrical nerve stimulation (TENS).

assessment score of patients with diagnosis of LS and MA was 2.5 (IQR 4) and 3 (IQR 1), respectively. In the group of LS and MA the median recurrence score after 2 months of the treatment was 0.5 (IQR 3) and 0 (IQR 1), respectively.

DISCUSSION

This is the first open-label trial in patients with LS and MA using DLQI as a pruritus measure, which confirms the findings of other studies that TENS is an effective treatment for pruritus.[1,14–16,18]

Findings from this study demonstrate that treatment with TENS is associated with beneficial impact in measures of DLQI and VAS scores in LS and MA-induced pruritus. Patient-reported outcomes including treatment assessment score also indicates that TENS is an effective therapy in the pruritus of LS and MA. It is clear that the efficacy of TENS began at week 2 both in LS and MA. Importantly, both DLQI total score and at least four DLQI subscales measure demonstrated TENS-induced improvement in two groups. Based on these results and the fact that all patients enrolled in the study had pruritus for at least 1 year, we suggest that TENS improves many different aspects that contribute to quality of life in patients with chronic pruritus.

The improvement on pruritus with therapy of TENS was maintained for up to 2 months. It is important to emphasize; however, that the duration of follow-up period was short. A longer time interval will be required to evaluate the long-term effects of TENS treatment.

The possibility that the observed improvements were attributable to a placebo effect would also need to be considered. Due to our study design (which involved no control group), we cannot completely eliminate the possibility of such a placebo effect, but we feel that the lack of pruritus recurrence during a post-treatment 2-month follow-up period suggests that a placebo effect is unlikely.

The effectiveness of TENS for pain relief has been well established but the exact mechanism is unclear. Some possible explanations have been proposed such as gate control theory, which was described by Melzack and Wall in 1965.[25] According to this theory, cells within the substantia gelatinosa are stimulated by both small-diameter nociceptive and large-diameter sensory neurons. These cells produce nociceptive impulses and serve as gates by inhibiting the relaying of nociceptive information to the brain if non-painful sensory stimuli (like a stimulation produced by TENS) are also present.

Based on currently available data suggesting that pain and pruritus are two sensations that share similarities both at the peripheral and central level, TENS could also provide antipruritic effect in itchy skin disorders.[14,26] So far, TENS has been reported to

offer pruritus relief in LS, generalized pruritus, atopic eczema, prurigo nodularis, mycosis fungoides and burns.[1,14–16,18,27] The putative mechanisms of the antipruritic action of TENS are as yet not clear. One possible mechanism is a peripheral nociceptive effect of electrical current on itching and pain fibers.[1]

A recent study reviewed the evidence of the efficacy of TENS for the treatment of LS.[1] The authors observed a significant amelioration of pruritus in most patients after 4 weeks, which was maintained for up to 1 month. In addition, the data reported in our study show improvement in pruritus of LS and also MA was initiated after 2 weeks of therapy and was maintained for up to 2 months. To the best of our knowledge, this is the first report of the use of TENS to alleviate pruritus in MA.

The safety profile in our study was similar to that reported in the previous studies.[14–16,27]Adverse event was observed in one patient with diagnosis of LS as local erythema at the side of the electrode application, which was transient. TENS treatment in LS and MA appears to be at least as safe as any alternative regimen.

To date, portable, mini-sized and microcomputer-processed TENS devices are easily available at reasonable prices and TENS is a simple, noninvasive technique that allows patients to use it on their own.

In summary, our results demonstrate that TENS provides significant improvement in itching and its impact on the patient's daily life. These improvements were observed in both patients with LS and MA. Moreover, a favorable safety profile was demonstrated in both groups. Our favorable experience suggests that TENS may be an alternative treatment for LS- and MA-induced pruritus and needs further investigation to examine its effect on pruritic dermatoses.

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