Effect of Acupuncture-like Electrical Stimulation on Chronic Tension-type Headache: A Randomized, Double-blinded, Placebo-controlled Trial

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Objective: The aim of this study was to examine the effect of acupuncture-like electrical stimulation on chronic tension-type headache (TTH) in a randomized, double-blinded, placebo-controlled study.

Methods: Thirty-six patients (18 men, 18 women) with chronic TTH in accordance with the criteria of International Headache Society were investigated. The patients were randomly assigned into 2 groups: a treatment group and a placebo group. Pain duration, pain intensity on a 0 to 10 cm visual analog scale, number of headache attacks, and use of medication were recorded in a diary for 2 weeks before treatment (baseline), early stage of treatment (Treat-1; 2 wk), late stage of treatment (Treat-2; 4 wk), and after the end of treatment (Post-1, Post-2, Post-3 corresponding to 2, 4, and 6-wk follow-up). The patients also provided an overall evaluation of the treatment effect at each stage. Patients were taught how to use either an acupuncture-like electrical stimulator or a sham stimulator (identical but incapable of delivering an electric current) and then instructed to use the device at home. Six acupoints, bilateral EX-HN5, GB 20, LI 4, were selected to be stimulated 3 minutes for each point, twice a day. Friedman repeated measure analysis of variance on rank was used to test the data.

Results: The pain duration was shortened at Treat-1 and pain intensity was decreased at Treat-1 and Treat-2 compared with baseline. The overall evaluation of the 2 treatments indicated improvements in both the treatment and the placebo groups, but with no significant difference between the groups ($P > 0.061$). Despite the apparent improvement in both the treatment and placebo groups, a decrease in analgesic use was only observed in the treatment group. There was also a significant positive correlation between the reported intensity of the stimulus-evoked sensation and the evaluation of the effect of either active or placebo treatments ($P = 0.039$).

Conclusions: The use of acupuncture-like electrical stimulation was not associated with significant adverse effects. These results indicate that acupuncture-like electrical stimulation is a safe and potentially analgesic-sparing therapy that may be considered as an adjunctive treatment for patients with chronic TTH although the clinical effect on pain seems to be marginal in the present set-up.

Key Words: acupuncture, chronic tension-type headache, randomized double-blinded placebo-controlled trial, visual analog scale

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The peripheral and central mechanisms of the tension-type headache (TTH) are still under discussion.[1] Acupuncture or electroacupuncture is widely used in the clinic for the treatment of TTH, and its effectiveness in relieving headache pain has been investigated.[2–6] Overall, the existing evidence suggests that acupuncture therapy could play a role treatment of recurrent headaches.[5,6] Various psychophysiologic and neurophysiologic mechanisms underlying the analgesic effectiveness of acupuncture have been hypothesized. A modification of the endorphinergic system has been suggested to account for modulation of nociceptive pathway,[7–9] or diffuse noxious inhibitory control (DNIC) system is suggested to be involved in the neuronal mechanisms.[10] The conclusions, however, are not unequivocal, generally due to the unsatisfactory quality of some studies and wide disparities in methodology.[4,6,11]

Finding an appropriate placebo control is the most difficult part of acupuncture research.[6] Acupuncture treatment is a physical, invasive, manual procedure, thus separating the specific effects from the nonspecific effects is extremely difficult. A realistic placebo control has therefore been a continuing problem for acupuncture research. Overall, 2 ways of control have been commonly used, either with insertion of needles into nonacupuncture points, so-called sham acupuncture[4,12] or without needle insertions, named placebo acupuncture.[13,14] However, with sham acupuncture there can be local effects, needling effects, as well as trigger point effects that may activate pain modulating systems to an unpredictable degree.[10,14,15]

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Alternatively, the lack of needle insertion in placebo acupuncture may cause patients to question the authenticity of the therapy.[6,16] As both sham and placebo acupuncture offer suboptimal placebo control, it is difficult to extract the degree of effectiveness of the bona fide acupuncture treatment, making the results of many studies less than fully convincing.[5]

Electroacupuncture, a combination of traditional Chinese acupuncture and electrical stimulation, uses electrical stimulation of the acupuncture points to produce therapeutic effects.[17] Different electrical parameters such as stimulation frequency, intensity, width of pulse, and interpulse interval can be adjusted to maximize therapeutic benefit. In addition, the problem of interpatient variability with regular acupuncture treatments are lessened with electroacupuncture, because it is possible to give all patients a standardized stimulus.[9] In the present study, a randomized, double-blinded, placebo-controlled trial was designed to evaluate the utility of a novel placebo electroacupuncture device in an investigation of the effect of acupuncture-like electrical stimulation on chronic TTH.

MATERIALS AND METHODS

Patients

Forty adult volunteer patients, 20 men and 20 women, with chronic TTH diagnosed in accordance with international criteria International Headache Society[18] were recruited for this study by making an announcement in the local news paper. Patients under the age of 18 or who also with migraine headache were excluded from the study. Four patients dropped out for personal reasons, 18 men and 18 women patients (mean age ± SEM: 45.3 ± 2.6 years) finished the study (Fig. 1). The study was conducted in accordance with the Helsinki Declaration and informed consent was obtained from all patients. The local ethics committee approved the study (VN 2001/128).

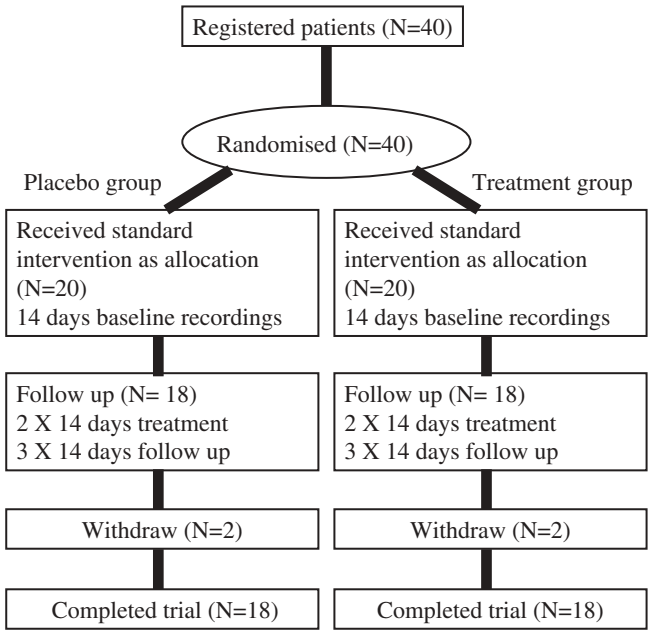

FIGURE 1. A flow diagram illustrates the study protocol.

Experimental Protocol

Patients were randomly assigned to the treatment or placebo group and given an active or placebo stimulator with a sequence code. The sequence code table was prepared and kept by the company (MibiTech ApS, Helsingør, Denmark) that supplied the stimulators. Neither the patient nor the clinical investigator was aware of this assignment. Pain duration, pain intensity, frequency of headache attack, and use of medication were recorded in a diary for 2 weeks before treatment (baseline), early stage of treatment (Treat-1; 2 wk), late stage of treatment (Treat-2; up to 4 wk), and after end of treatment (Post-1, Post-2, Post-3) corresponding to 2, 4, and 6 weeks follow-up. The patients also provided an overall evaluation of the treatment effect at each stage. An acupuncture-like electrical stimulator or a placebo stimulator was used by patients at home.

After completion of the experimental part of the study, the clinical examiner was given only sufficient information to separate the patients into 2 groups, that is the randomization code was unsealed, but the investigator was not given information about the actual treatment that the groups received. A blinded statistical analysis of the results was then performed by the investigator on the 2 groups, after which the final randomization code for treatment was broken.

Acupuncture-like Electrical Stimulator

An electrical stimulator or placebo stimulator (TAO, MibiTech ApS, Helsingør, Denmark) was used by patients at home after careful instructions.[19] Six acupoints, bilateral EX-HN5, GB 20, LI 4, were selected to be stimulated 3 minutes for each point, twice a day. The location of these points was shown to each patient in a face-to-face meeting with the clinical examiner, and an illustration of the location of these points was given the patient to take home. The active stimulator is "pen-shaped" with a tip diameter of 1 mm and has an output of 25 V, with an alternative frequency of 2 and 100 Hz at 3 seconds intervals. The duration of each square wave pulse is 5 and 0.7 ms, respectively. The stimulator's output of alternating low (2 Hz) and high frequency (100 Hz) at a 3-second interval is based on research that indicates this dense-and-disperse design has the best analgesic effects of electroacupuncture in experiments and clinical applications.[20,21] Stimulation was indicated with a green flash. The placebo stimulator had the exact same shape and color as the active one, as well as the green flash during the operation, however, without any output.

Six acupuncture points were selected according to the traditional Chinese acupuncture principle.[22] Combining the technique of transcutaneous electrical stimulation, we used a "handle pen" instead of needles to stimulate the

acupuncture points, which is also called needle-free electroacupuncture.[9] With appropriate stimulation parameters, it can produce the same analgesic effect.[9] The medium myelinated A-β and A-δ fibers are expected to be activated during the electrical stimulation to elicit the sensation of "de qi."[23]

Outcome Parameters

Duration of headache pain was calculated as hours with headache on each day. Pain intensity was scored on a 0 to 10 cm visual analog scale with the lower extreme marked "no pain" and the upper extreme marked "most pain imaginable." The patients were furthermore asked to draw the area of pain and describe the quality of pain on a Danish version of the McGill Pain Questionnaire at each stage. The pain rating indices of the sensory, affective, evaluative, and miscellaneous dimension of pain were calculated in accordance with Melzack.[24] The frequency of headache attack and medicine consumption was recorded.

The patients also provided an overall evaluation of the treatment effect at each stage on a 6-point scale from −2 to +3 (−2: much worse; −1: a little worse; 0: no change; +1: a little better; +2: much better; +3: no more pain).

Finally, the intensity of the stimulus-evoked sensation during the treatment was scored by the patients on a 4-point scale, with 0 to 3 (0: no sensation; 1: slight sensation; 2: strong sensation; 3: painful sensation).

Analysis

Friedman repeated measure analysis of variance on rank was performed and followed by pair-wise multiple comparisons (Tukey test). A *t*-test was used to compare the 2 groups. The effect size and the mean differences between 2 groups with their 95% confidence intervals (CIs) are given in the Results section. Spearman rank order correlations were used to test the associations between the stimulus-evoked sensation and overall evaluation of effect. The level of significance was set at $P < 0.05$.

RESULTS

Headache Pain Description

All 36 patients recruited in the study had experienced headache more than 16 days a month. The headache pain was described as "pressing" (24/36), "taut" (23/36), "hurting" (20/36), and "exhausting" (18/36). The pain was located on the front, back, and temporalis area of head, most spread toward the neck (23/36), and some toward the jaw muscles (6/30). The PRIs of sensory (S), affective (A), evaluative (E), miscellaneous (M) dimension of pain were S = 6.0 ± 0.6, A = 2.4 ± 0.3, E = 0.8 ± 0.1, M = 1.9 ± 0.3.

There were no significant differences between 2 groups with age (*t*-test: $P = 0.376$), pain history ($P = 0.370$), daily pain duration ($P = 0.081$), or pain intensity ($P = 0.218$). The baseline information for all patients who completed the study is summarized in Table 1.

After treatment, 2/36 patients reported that their headache pain had been totally relieved, 4/36 patients felt much better, 7/36 patients felt slightly better, 22/36 patients felt no change, and 1/36 patients felt slightly worse (Table 2).

Daily Headache Duration

A 1-way repeated ANOVA showed that there was a time effect on daily headache duration in the treatment group. It indicated a 30% reduction at Treat-1, 17% at Treat-2, and 13% at the end of recording of Post-3 in the treatment group. It also indicated a 14% reduction at Treat-1, 12% at Treat-2, and 12% at the Post-3 in the placebo group. However, a direct comparison of the changes in headache duration between the treatment and placebo group was not significant ($P > 0.253$) with a change from 8.6 ± 7.4 to 6.0 ± 7.7 (effect size: 0.34; 95% CI: −7.67 to 2.54) in the treatment group and 9.8 ± 8.0 to 8.4 ± 8.9 (effect size: 0.17; 95% CI: −4.34 to 7.14) in the placebo group (effect size: 0.41; 95% CI: −0.11 to 0.45). In the posttreatment period the differences between the treatment and placebo group became less apparent (see Fig. 2A).

Average Headache Intensity

The average headache intensity was lower at Treat-1 and Treat-2 compared with the baseline. The pain intensity decreased from 4.9 ± 1.1 to 3.9 ± 1.6 at Treat-1, and to 3.3 ± 1.8 at Treat-2 in the treatment group. The effect size was 0.73 (CI: −1.93 to −0.08) and 1.03 (CI: −2.58 to −0.53). The pain intensity also decreased from 5.4 ± 1.5 to 5.1 ± 1.7 at Treat-1, and to 5.1 ± 2.0 at Treat-2 in placebo group and the effect size was 0.58

TABLE 1. Baseline Information for All 36 CTTH Patients

	Age (y)	Pain History (y)	Pain Duration (h)	Pain Intensity (0 to 10 cm)	Attacks/2 wk (Numbers)	Medication/2 wk (Numbers)
Placebo						
Men: 8	51.5 ± 7.4	19.6 ± 8.5	7.9 ± 1.9	5.7 ± 0.6	10.5 ± 1.4	26.1 ± 14.7
Women: 10	54.9 ± 3.9	20.5 ± 3.9	9.7 ± 1.6	4.3 ± 0.6	11.8 ± 3.1	31.7 ± 10.0
Acupuncture						
Men: 10	47.2 ± 4.7	14.3 ± 3.9	9.3 ± 2.8	3.9 ± 0.6	9.2 ± 1.4	29.2 ± 7.9
Women: 8	38.3 ± 4.7	9.4 ± 1.0	7.7 ± 1.9	5.0 ± 0.3	12.8 ± 1.6	25.1 ± 8.8

CTTH indicates chronic tension-type headache.

TABLE 2. Overall Effect Evaluation by All Patients at the End of the Treatment

	No Pain	Much Better	Little Better	No Change	Little Worse	Much Worse
Placebo						
Men: 8	0	0	1	7	0	0
Women: 10	1	1	3	4	1	0
Acupuncture						
Men: 10	1	0	3	6	0	0
Women: 8	0	3	0	5	0	0

(CI: −0.15 to 2.02) (Fig. 2B). However, there was no significant difference in pain intensity changes between the 2 groups ($P > 0.061$). The effect size was 0.57 and the mean difference between group was < 16% (CI: −0.03 to 0.34).

Frequency of Headache Attacks

The number of headache attacks in the 2 weeks during the treatment was slightly decreased from 10.5 ± 4.6 to 9.5 ± 5.9 at Treat-1 and to 8.4 ± 5.7 in the treatment group. The effect size was 0.47 (CI: −8.08 to 1.48). There were also slight decreases from 11.5 ± 4.0 to 10.6 ± 3.8 at Treat-1 and to 10.7 ± 3.8 in the placebo group. The effect size was 0.23 (CI: −1.74 to 3.54) (Fig. 2C). Again, there were no significant differences between the 2 groups ($P > 0.169$) and the effect size was 0.47 and the mean difference between the groups was < 12% (CI: −0.3 to 0.06).

Use of Medication

The 2-week consumption of analgesics decreased from 26.1 ± 23.3 to 16.9 ± 22.9 at Treat-1 in treatment group. The effect size was 0.40 (CI: −8.10 to 6.44). There were no apparent changes in analgesic consumption at any stage in the placebo group (Fig. 2D). The mean difference between the groups was < 34%, and the effect size was 0.57 (CI: −0.75 to 0.06). The direct comparison between the 2 groups did, however, not indicate any significant differences ($P > 0.095$).

Overall Evaluation

The patients' overall evaluation of the effect on the headache was improved compared with baseline in both treatment and placebo groups. The effect size in the treatment group was 1.01 (CI: 0.17 to 0.88) at Treat-1 and 0.97 (0.19 to 1.09) at Treat-2. The effect size in the placebo group was 0.68 (CI: 0.0 to 0.56) at Treat-1 and 0.70 (CI: 0.02 to 0.93) at Treat-2. A direct comparison of the 2 groups showed a mean difference between groups was 25% and the effect size was 0.37 (CI: −0.2 to 0.7) ($P > 0.264$).

Intensity of Stimulus-evoked Sensation

There were 6/18 patients who felt a slight sensation and 2/18 felt strong sensation in the placebo group; whereas 9/18 felt a slight sensation and 1/18 a strong sensation in the treatment group. There was no significant difference between the 2 groups ($P > 0.766$) during Treat-1 and Treat-2. None of the patients reported unpleasant effects that they associated with use of either electrical or placebo stimulator. There was, however, a significant correlation between the stimulus-evoked sensation and the overall effect evaluation (Spearman rank order: $R = 0.346$, $P = 0.039$).

DISCUSSION

In the present study, the effect of acupuncture-like electrical stimulation on chronic TTH was compared with

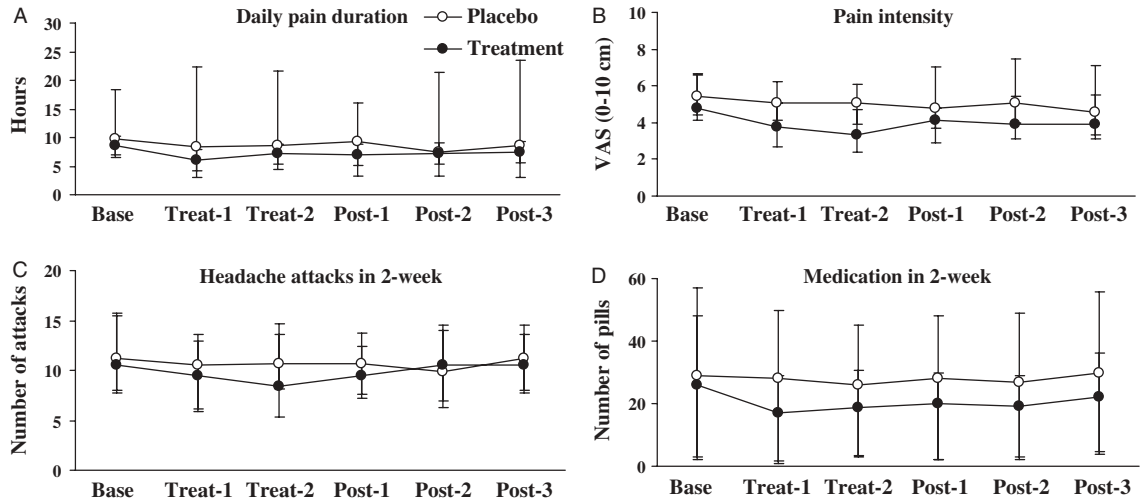

FIGURE 2. Averaged treatment effect of 2 groups at different stages. A, Daily headache pain duration; B, Headache pain intensity; C, Headache attacks over the 2-week period; D, Use of medication during the 2-week period (number of pills). Median values+interquartile ranges (n = 18).

a placebo control. It was found that compared to baseline levels, headache intensity, duration, and frequency were all marginally decreased in both the treatment and placebo groups. This improvement in headache pain parameters was associated with a decrease in the use of analgesic medications by the treatment group. Nevertheless, it is important to recognize that there was a nonsignificant trend toward improvement in the pain scores of the placebo group as well, although this was not associated with an altered use of analgesic drugs. Significant differences between the treatment and the placebo groups were not detected. Overall effect evaluation was significantly correlated to the intensity of stimulus-evoked sensation.

Study Limitations

The results of this study suggest that patients would not likely be able to differentiate between the electroacupuncture stimulator and the placebo, but that treatment with the placebo stimulator improved headache pain ratings (Table 2). Even though there was no electrical output from the placebo stimulator, when the handle pen was pressed on the acupuncture points during placebo treatment, some patients reported a slight sensation (6/18) and others a strong sensation (2/18). The number of individuals in the placebo group who reported feeling a sensation was similar number of the patients in the treatment group who reported a slight (9/18) or strong sensation (1/18) during stimulation. The mechanical stimulation of the acupoints with the active or placebo stimulator may have had an "acupressure"-like effect,[25] which also could elicit the de qi sensation. The de qi is a sensation of numbness, tingling, or tenderness, which has been associated with the activation of A-δ afferent fibers and may be responsible for the effectiveness of acupressure therapy.[11,26] Because of the mechanical pressure applied from the handle pen, the placebo acupuncture may mimic the nonspecific physiologic effect of the real acupuncture, which may have resulted in a smaller difference between treatment and placebo groups. It has been noted that placebo acupuncture has an analgesic effect about 40% to 50% of real acupuncture.[2] Therefore, although the placebo treatment in this study was well "blinded," the possibility that the placebo may also have exerted a positive therapeutic effect on headache pain may explain the lack of significant difference between the placebo and treatment groups with regard to headache pain and intensity.

Another limitation of this study was the use of a fixed intensity of electrical stimulation in all patients in the treatment group. Our results indicate that patients who perceived the stimulus during therapy were more likely to rate the overall treatment as effective. Traditional Chinese acupuncture emphasizes an individualized treatment and uses different acupuncture points and stimulation intensities for varying disease states and patient characteristics.[22] When the acupuncture points are being stimulated, the patients can sense a special acupuncture de qi sensation with "aching," "tingling," and "distending." The de qi sensation seems to play an important role in acupuncture analgesia. Animal research has shown that electroacupuncture analgesia increases as the stimulus intensities increase.[25] In human studies, a greater improvement of pain has been shown if the practitioner tends to provide more of a contrast to the placebo needle.[16] On the basis of de qi sensation concept of traditional Chinese acupuncture, it would appear that the intensity of the acupuncture-like electrical stimulation for a majority of the patients was likely suboptimal.

A third limitation of this study was the relatively small sample size. Given the large diversity of headache symptoms in our patient population, it is conceivable that our sample of 36 individuals were insufficient to accurately reflect the population characteristics of TTH sufferers. Recently, 2 larger controlled studies, which investigated 74 and 270 patients, respectively, have shown a significant effect of acupuncture on chronic tension-type headache patients.[27,28] A well-planned placebo-controlled study with an increased number of patients should be considered to assess the effectiveness of acupuncture on chronic TTH.

Underlying Mechanisms

Although the exact pathophysiologic mechanisms of TTH are still unclear, it has been hypothesized that peripheral sensitization may contribute to the development of TTH.[29,30] Pericranial muscle tenderness, which can be found in a lot of people with headache,[31–33] is the most apparent abnormality in patients with TTH[31] and has been shown to be highly correlated to the intensity of TTH.[32] Various noxious and innocuous mechanical stimuli, ischemia, and certain chemical mediators can excite and sensitize A-δ fiber and C-fibers which innervate muscle tissue, and thus play a role in the increased tenderness in TTH.[34,35] Stimulation of the acupuncture points has been speculated to elicit a local tissue effect with improved blood circulation and relaxation of local tender points in the muscles.[3,36] Increased muscle blood flow could contribute to decreased pain in tender points by reversing local ischemia and/or hastening the clearance of sensitizing chemicals.

Other researchers have reported that the central nerve system is hypersensitive to painful stimuli in TTH patients.[37] Sensitization of second-order nociceptive neurons at the level of the spinal dorsal horn and/or trigeminal subnucleus caudalis, sensitization of supraspinal neurons, and decreased antinociceptive activity from supraspinal structures also may play an important role in headache pain.[38] Neurophysiologic studies in animals and humans provide evidence that acupuncture increases the threshold of nociceptive neurons to peripheral stimulation and works by increasing the levels of certain endogenous opioids and/or other neurotransmitters.[20] The possibility that this may involve activation of the DNIC system has been discussed.[9,36,39] DNIC is the phenomenon whereby noxious stimulation in one part of

the body inhibits the response to noxious stimulation in another part of the body and is thought to be mediated, in part, through activation of endogenous opioidergic pathways.[40,41] However, the hypothesis that DNIC is responsible for sham or even real acupuncture analgesia is debatable because the effects of DNIC tend to be transient disappearing after ceasing heterotopic stimulus application.[26]

CONCLUSIONS

Acupuncture-like electrical stimulation might have some promising effects on TTH-related pain and importantly seems to reduce the use of analgesic agents in people with TTH but the effect is difficult to differentiate from a placebo control. The placebo stimulator also seemed to exert some positive effect, however, analgesic use in this group remained unchanged, which may indicate that patients in the placebo group were underreporting the severity of their pain symptoms. A larger study might demonstrate a statistically significant effect of treatment between the 2 groups. Perceived stimulation intensity seems to be the key factor in the effectiveness of treatment with this stimulator and thus future study should be designed to individualized stimulation to provide optimal treatment. As the use of acupuncture-like electrical stimulation was not associated with significant adverse effects on its own, we suggest that this technique is a safe and potentially analgesic and side effect-sparing therapy that can be attempted as an adjunctive treatment for patients with chronic TTH, but it needs to be kept in mind that the effect on pain seems to be very modest.

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