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The analgesic effects of transcutaneous electrical nerve stimulation and placebo in chronic pain patients

A double-blind non-crossover comparison

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Summary. The analgesic effects of high frequency transcutaneous electrical nerve stimulation (TNS), "acupuncture-like" TNS and placebo TNS were evaluated in 33 patients with rheumatoid arthritis and chronic hand pain using a randomized, double-blind, non-crossover design. An oscilloscope was employed to monitor the stimulator output in the TNS treatment groups and to provide strong suggestion and a focus of attention in the placebo treatment group. The two forms of TNS were applied at the highest intensity that could be tolerated by patients. Assessments of resting pain, joint tenderness, grip strength and grip pain were made before and after treatment. The pain and joint tenderness measurements showed high frequency TNS, "acupuncture-like" TNS and placebo TNS to be equally effective in producing analgesia of similar degree and trend over time. The grip strength measurements showed no significant change. The results obtained with placebo are probably due to the suggestion and attention effects of the visual stimulus. The implications of these results in respect to pain control pathways are discussed. Although TNS given at high intensity was shown to be no better than placebo applied with strong suggestion, this does not preclude its use as a method of pain control in rheumatoid arthritis.

Key words: Transcutaneous electrical nerve stimulation – Placebo – Chronic pain

Introduction

The gate control theory [1] first introduced the concept of pain modulation via descending inhibitory nerve pathways. Subsequent investigation showed that the descending pain control system was most effectively activated by noxious input transmitted predominantly by small-diameter fibres [2]. Noxious stimulation, though initially giving rise to pain, activates the descending control system to close the gate at the level of the dorsal horns, thereby inducing pain relief. High intensity (noxious) transcutaneous electrical nerve stimulation (TNS) was developed as a physical means of activating the descending control system to modulate pain. There are three types of high intensity TNS in use: high frequency, low frequency, and "acupuncture-like".

Before any new analgesic is released for therapeutic use it is considered essential to determine whether its effect is equal to or greater than placebo [3]. This has proved difficult in studies of electrical stimulation because of the unavailability of a placebo indistinguishable from TNS [4]. Placebo TNS is usually administered with a sham stimulator that delivers no electric current [3, 5, 6]. Patients can easily distinguish the placebo from the intrinsic tingling sensation of TNS, so crossover studies are inappropriate and will produce incorrect conclusions [7]. The tingling effect of TNS also acts as a focus of attention which might contribute to the pain relief [7]. The influence of attention on pain perception has been noted previously [8].

A recent double-blind non-crossover study found that high frequency TNS was more effective in relieving chronic pain than a placebo presented in a neutral manner. However, it was considered that the suggestion associated with TNS was much greater than that associated with placebo, in so much as a placebo applied with equal suggestion might produce comparable effects [9]. Placebos are known to produce analgesia [10] and have been found to be efficacious in approximately 35% of patients [11, 12]. A recent review has reported an incidence of placebo effectiveness varying between 1 and 69% [13].

The purpose of the present study was to compare the pain relieving effects of placebo TNS, high frequency TNS and "acupuncture-like" TNS in patients with rheumatoid arthritis and chronic hand pain. A visual stimulus was incorporated to provide strong suggestion and act as a focus of attention for patients receiving sham stimulation.

Materials and methods

Patients. Thirty-three outpatients with classic or definite rheumatoid arthritis (ARA criteria) and chronic hand involvement

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consented to participate in the study. Entry required that patients had pain present in one or both hands. If they had pain in both hands, the one considered most painful was treated. Patients under the age of 18 years or with any form of heart condition were not admitted. A standard neutral statement concerning the effects of TNS was read to all patients. Patients were instructed to stop taking their anti-inflammatory analgesics 24 h prior to the study, but to resume afterwards.

Experiment. A randomized, double-blind, non-crossover design was used. On entry to the study patients were assigned to one of three treatment groups by observer PS. Each group, consisting of 11 patients, was matched for mean age and duration of disease. Group A received 20 min of high frequency TNS, Group B received 20 min of "acupuncture-like" TNS and Group C received 20 min of placebo TNS. Observer PS administered the treatment to patients from the respective groups in a randomized manner. A different observer (GL) carried out measurements on the hand before and after treatment. Neither the patients nor observer GL knew which treatment had been administered by observer PS.

A Grass Model S48 Square Wave Stimulator and Grass Stimulus Isolation Unit were used to deliver monophasic pulses via two surface electrodes. The electrodes, a wet pad type with surface area of 9.08 cm^2, were placed immediately proximal to the patients wrist, with one electrode on the volar surface and the other on the palmar surface. For Group A, the stimulator was set to deliver continuous square wave pulses of 0.2 ms duration and frequency of 100 Hz; for Group B the stimulator was set to deliver a 2 Hz train of square wave pulses with an internal frequency of 100 Hz and duration of 70 ms. For both TNS groups the stimulation intensity was the highest that could be tolerated by the patient. Patients in Group C did not receive electrical stimulation as observer PS had turned a hidden switch so that no current reached the electrodes. The stimulator output was shown to patients receiving TNS on a Hitachi Model V-152B Oscilloscope. Although no electrical current was actually administered to Group C, a random pattern of pulse waves was generated on the oscilloscope screen as if current was being delivered.

Assessments. A total of seven assessments were carried out on the hand undergoing therapy, one pre-treatment and six post-treatment. The post-treatment assessments were given at 15 min intervals. Each assessment consisted of four measurements administered in the following order; pain at rest, joint tenderness, grip strength, pain while gripping.

Pain at rest and pain while gripping were measured using 10 cm vertical visual analogue scales. The scale endpoints consisted of "no pain" and "worst pain ever". Patients were required to place a mark on the line between the two extremes indicating the degree of pain in their hand at rest and while gripping. The pain scores were calculated at the end of the study by transposing a 22-point linear scale over the visual analogue scales. The number corresponding to the patients mark on the visual analogue scale was recorded as the pain score.

Joint tenderness was evaluated using the pressure dolorimeter [14] which scores tenderness on a 22-point logarithmic scale. Fifteen joints were assessed; the wrist, metacarpophalangeal, proximal interphalangeal and distal phalangeal joints. Increasing pressure was gradually exerted perpendicular to the joint margin until either, a standard maximal pressure of 67.6 Kpa was reached or the patient indicated tenderness in the joint, at which point the scale was read and the tenderness score recorded. Pressure was applied to one surface of the joint only, the opposite surface being flat against, or in the case of flexion deformities on the edge of, a non-compressible object. The method allows the calculation of two indices; total joint tenderness (A) and total number of tender joints (B).

Grip strength was measured using the modified method [15] which electronically records and expresses grip strength as power (watts) and maximum work done (joules). Patients were required to squeeze a large conical bag containing approximately 3 litres of air, as hard and fast as possible. Five squeezes of the bag were performed at each assessment, the maximum power and work done being recorded. It was anticipated that relief of hand pain would result in an increase in gripstrength.

Data analysis. For the measures of resting pain, grip pain, total joint tenderness (A) and total number of tender joints (B), the within group differences were evaluated using the Wilcoxon sign rank test and the between group differences using the Mann-Whitney *U*-test.

For the measures of maximum power and work done, the within group differences were evaluated using the paired *t*-test and the between group differences using the two-sample *t*-test.

Results

The details of patients in each treatment group are given in Table 1. The mean pre-treatment or baseline scores for the pain, tenderness and grip strength measurements are shown in Table 2. No significant differences were found between groups for any of the baseline scores.

The high frequency, "acupuncture-like" and placebo TNS groups all demonstrated a noticeable decrease in mean scores for resting pain and grip pain following treatment (Figs. 1 and 2). No significant differences were found between the groups at any of the post-treatment assessments. The percentage of patients within each group reporting significant (50% or more) relief of resting pain and pain while gripping was calculated (Table 3). These

Table 1. Patient details for each treatment group. *A* high frequency TNS; *B* "acupuncture-like" TNS; *C* placebo TNS

Parameter	Treatment group		
	A ($n=11$)	B ($n=11$)	C ($n=11$)
Male	4	1	4
Female	7	10	7
Classic RA[a]	7	4	3
Definite RA[a]	4	7	8
Mean age in years (SD)	54.9 (15.3)	53.7 (15.9)	53.4 (14.1)
Mean duration of disease in years (SD)	11.3 (7.5)	11.7 (9.3)	10.7 (10.7)

[a] American Rheumatism Association Criteria

Table 2. Baseline measures for each treatment group. *A* high frequency TNS; *B* "acupuncture-like" TNS; *C* placebo TNS

Baseline measure	Treatment group		
	A ($n=11$)	B ($n=11$)	C ($n=11$)
Mean resting pain (SD)	8.8 (4.2)	7.3 (4.0)	9.2 (5.0)
Mean total joint tenderness (A) (SD)	26.4 (30.7)	59.3 (73.0)	46.9 (41.6)
Mean total number of tender joints (B) (SD)	7.9 (5.5)	10.1 (5.0)	10.1 (4.7)
Mean power (SD)	1.0 (0.9)	1.2 (1.7)	2.2 (2.0)
Mean work (SD)	0.4 (0.3)	0.5 (0.7)	0.7 (0.7)
Mean grip pain (SD)	12.3 (4.5)	9.6 (5.7)	11.7 (4.8)

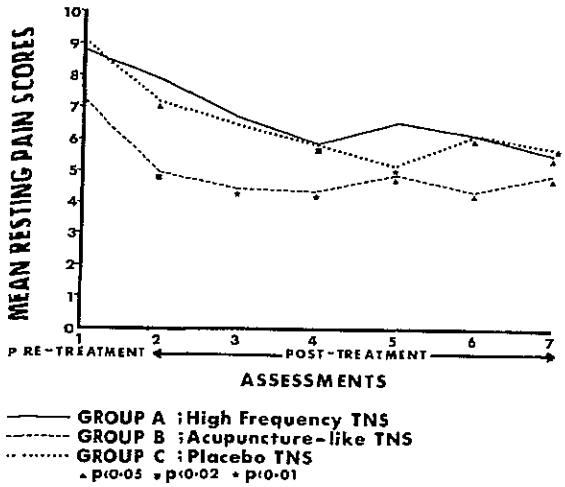

Fig. 1. Mean resting pain scores for each treatment group ($n=11$) at each assessment. Decreasing values indicate pain relief

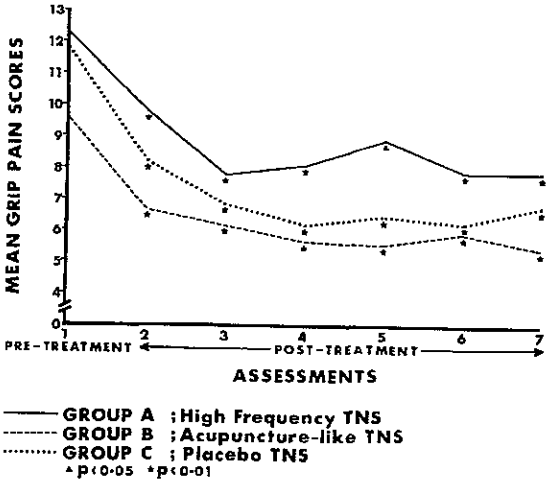

Fig. 2. Mean grip pain scores for each treatment group ($n=11$) at each assessment. Decreasing values indicate pain relief

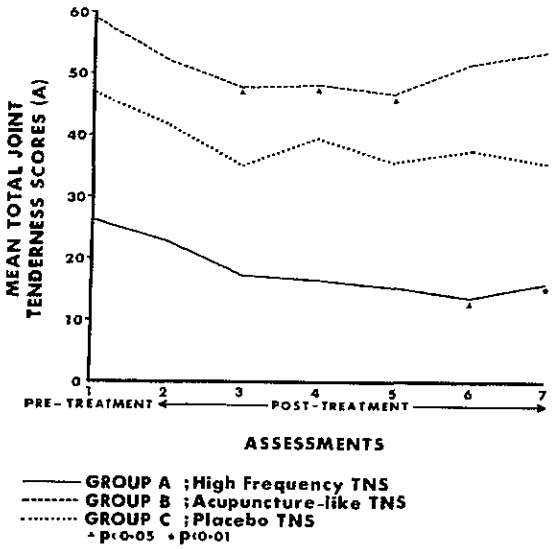

Fig. 3. Mean total joint tenderness scores (A) for each treatment group ($n=11$) at each assessment. Decreasing values indicate tenderness relief

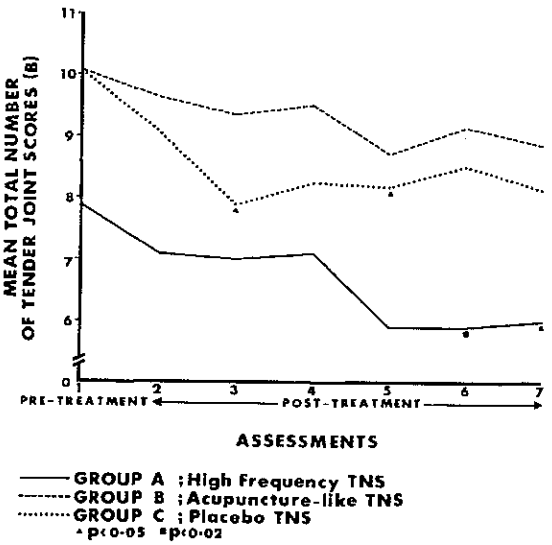

Fig. 4. Mean total number of tender joint scores (B) for each treatment group ($n=11$) at each assessment. Decreasing values indicate tenderness relief

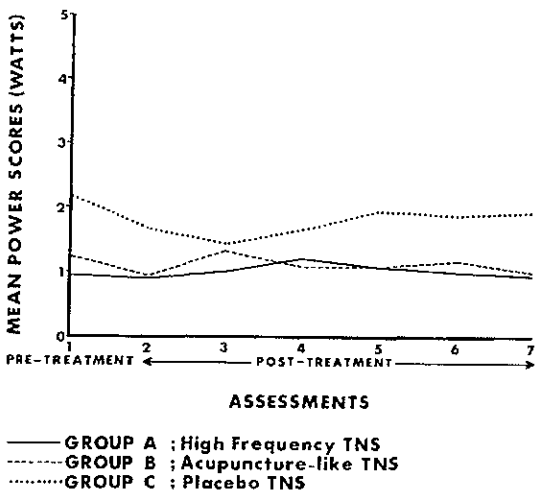

Fig. 5. Mean power scores for each treatment group ($n=11$) at each assessment. Increasing values indicate improvement

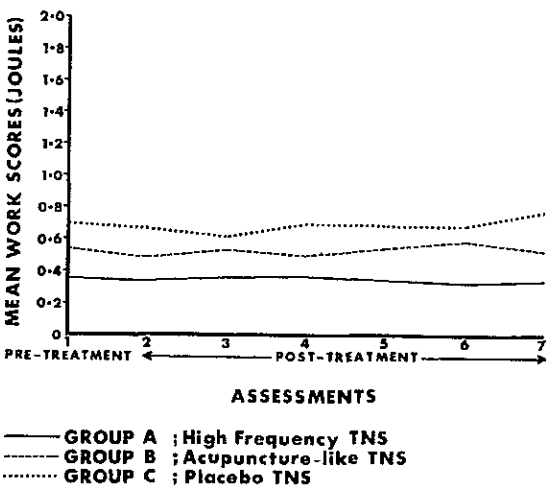

Fig. 6. Mean work scores for each treatment group ($n=11$) at each assessment. Increasing values indicate improvement

Table 3. The percentage of patients within each treatment group reporting significant (50% or more) relief of pain and tenderness. *A* high frequency TNS; *B* "acupuncture-like" TNS; *C* placebo TNS

Measurement	Percentage of patients with significant relief		
	A ($n=11$)	B ($n=11$)	C ($n=11$)
Resting pain	54.5	63.6	36.6
Grip pain	63.6	63.6	72.7
Overall pain relief[a]	59.0	63.6	54.6
Total joint tenderness (A)	63.6	54.4	63.6
Total number of tender joints (B)	45.4	27.3	45.4
Overall tenderness relief[a]	54.5	40.9	54.5

[a] Overall relief figures are referred to throughout the text

percentages were averaged (overall pain relief) and found to be similar for each treatment group (Table 3).

All three groups showed an improvement in mean total joint tenderness scores (A) (Fig. 3) following treatment, but this was not statistically significant in the placebo TNS group. Similarly, all three groups showed an improvement in mean total number of tender joint scores (B) (Fig. 4) following treatment. This improvement did not attain statistical significance in the "acupuncture-like" TNS group. Comparison of treatment groups revealed no significant differences at any of the post-treatment assessments. The percentage of patients within each group reporting significant (50% or more) relief of total joint tenderness and total number of tender joints was calculated (Table 3). These percentages were averaged (overall tenderness relief) and found to be similar for each treatment group (Table 3).

Although the duration of analgesia was not determined beyond the 1.25 h study period, patients reported relief of pain and tenderness up to the final assessment and showed no tendency to return to baseline scores.

The mean power and work scores did not alter significantly following treatment in any of the groups (Figs. 5 and 6). Consequently, no significant differences were found between the groups at any of the post-treatment assessments.

No adverse side-effects were reported by patients receiving TNS or placebo.

Discussion

High frequency TNS, "acupuncture-like" TNS and placebo TNS were found to be equally effective in producing analgesia of similar degree and trend over time. These findings are consistent with those of previous workers investigating the pain relieving effects of TNS and placebo in chronic pain patients [3]. However, they concluded that TNS was more effective than placebo on the basis of the percentage of patients reporting a partial or complete relief of pain. This was not supported by the findings of the present study where the percentage of patients reporting 50% or more pain relief was similar in the TNS and placebo treated groups. The duration of relief produced by each treatment was not determined, but has been shown to persist up to 46 h following both TNS and placebo [3]. High frequency TNS, "acupuncture-like" TNS and placebo TNS also decreased tenderness, though the benefit achieved was not as marked as that for pain. These results demonstrate that TNS and placebo relieve two characteristic symptoms of inflammation. The tacit assumption that grip strength improves when hand pain decreases was found to be incorrect. Power and work measures showed no significant change following TNS and placebo treatment, which suggests that grip strength is an unsatisfactory indicator of pain relief. However, the act of gripping served to bring out pain not present at rest making the effects of TNS and placebo more discernable.

The findings of the present study demonstrate the complexity and power of the placebo effect. An oscilloscope displaying pulse waves was used during TNS and sham therapy in an attempt to equate the attention and suggestion properties of placebo with those intrinsic to TNS. The display suggested to patients in the placebo group that electrical stimulation was being given and functioned as a focal point to draw their attention away from their pain and tenderness. Patients receiving TNS could attend to either the sensory effects of stimulation or the visual display instead of their pain and tenderness. It has been previously noted that providing a focus of attention can markedly influence pain perception [8]. The obvious focus used in the present study probably accounts for the similar results obtained in each treatment group and partially explains the superiority of TNS in an earlier study when a less obvious focus was used in the placebo group, i.e. a red diode switched on [9].

The positive placebo response rate of 54.6% for pain, though higher than that reported by Beecher [11] and Shapiro [12] is in accord with the findings of previous reports [13, 16]. Furthermore, it has been shown that patients with chronic painful diseases, such as rheumatoid arthritis, are more likely to respond positively to placebo therapy [10, 16, 17]. The beneficial effects recorded by patients in the placebo group indicate that they have the psychological capacity to control their own pain and tenderness and that they possess a positive attitude towards therapy. Whereas the detrimental effects of placebo given with strong negative suggestion have previously been described [18], the scope for benefit of placebo given with strong positive suggestion has not been systematically studied. In addition to their therapeutic effects, placebos can mimic many of the other properties of active pharmacological agents, e.g. a time-effect curve, a cumulative effect and carry-over effects [19]. Patients also become addicted to placebos and show many of the formal traits of drug dependence [20].

A specific opiate antagonist, naloxone, has been found to inhibit the pain relieving effects of "acupuncture-like"

TNS [21] but not to counteract the analgesia produced by high frequency TNS [21, 22]. Recent work has indicated that the descending pain control system contains parallel modulating lines, one naloxone sensitive, i.e. endorphin mediated, and the other naloxone insensitive, possibly serotonin mediated [2]. Consequently, high frequency TNS is considered to be mediated via the naloxone insensitive pathway, and "acupuncture-like" TNS via the naloxone sensitive pathway. Placebo analgesia has been reversed by nalaxone in some studies [23, 24] but not in another [25]. It would appear the placebo can induce analgesia via either the nalaxone sensitive or insensitive pathways of the descending control system. The similarity in the degree of analgesia produced by high frequency TNS, "acupuncture-like" TNS and placebo TNS suggests that the naloxone sensitive and insensitive pathways of the descending control system are equally effective in releaving pain by suppressing activity in the small-diameter fibres and closing the gate at the level of the dorsal horns. Increased knowledge of the physiology and biochemistry of placebo may eventually lead to its optimal use as a means of pain control.

In conclusion, the results of this study have shown that TNS given at high intensity is no better than placebo applied with strong suggestion. This does not preclude the use of TNS to relieve pain and tenderness in patients with rheumatoid arthritis as it is effective, non-invasive and free of side effects. The results also provide greater insight into the pain relieving effects of placebo, a potent intervention in its own right.

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