



Evaluation of therapeutic effect of transcutaneous electrical acupoint stimulation on bone metastasis pain and its influence on immune function of patients

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Background: This study aimed to observe the effect of transcutaneous electrical acupoint stimulation (TEAS) on bone metastasis pain, anxiety and immune function in cancer patients.

Methods: A total of 127 patients with bone metastasis pain from malignant tumors were treated with TEAS or drugs. The TEAS group comprised of 62 patients, while the drug control group comprised of 65 patients. The differences in general indexes, baseline pain and anxiety between these two groups were not statistically significant.

Results: Compared with those before treatment, the visual analog scale (VAS) scores of patients in the TEAS group and drug control group decreased after treatment, and the differences were statistically significant. The degrees of pain relief after treatment were similar between the two groups. Anxiety improved in both the TEAS group and drug control group, and the difference between these two groups was not statistically significant. The differences in immune indexes, B cell and CD8 between the TEAS group and drug control group were statistically significant. TEAS treatment could improve the declining trend of CD8 in patients.

Conclusions: TEAS treatment and drug treatment can effectively alleviate mild to moderate pain in patients, and the efficacy of these two groups is similar. The treatment for moderate and severe pain needs to be combined with drug treatment to achieve a control effect. TEAS can improve the anxiety and immune function of patients, and prevent the decrease in B cells and CD8 in patients treated with drugs alone.

Keywords: Transcutaneous acupoint electrical stimulation; cancerous pain; tumor; immunity; clinical research

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Introduction

Cancer pain remains as the focus and a challenge in cancer treatment. Opioids are the best choice for chronic moderate to severe cancer pain, but these are not omnipotent. Some patients suffer from bone metastasis pain due to invasion of the bone or periosteum by tumors. Hence, these patients need non-steroidal drugs, antidepressants, convulsants, and

even nerve ablation. Meanwhile, patients have unavoidable side effects, such as constipation, vomiting and dizziness. With the increase in dosage, the side effects further increase, which limit the application of these drugs.

Transcutaneous electrical acupoint stimulation (TEAS) is a peripheral stimulation. It is an electrotherapy method for relieving pain by delivering low-frequency pulsed

current to the human body through the skin. Electrodes are mostly placed on specific acupoints, which can produce acupuncture-like effects. Frequency conversion and different current intensity are commonly used in clinical application, in order to make the TEAS produce a variety of stimuli, inducing the central nervous system to secrete enough analgesic substances to achieve better therapeutic effects (1-8). Preliminary studies have been carried out to explore this mechanism (5,9-13). However, most of these clinical trials are not randomized enough, and there was no control group. Hence, these are far from the present requirements of evidence-based medicine (14,15). Therefore, the present study was designed based on the unsatisfactory therapeutic effect of bone metastasis cancer pain treatment, with the aim of improving the therapeutic effect of bone metastasis cancer pain by taking advantage of the skin-sticking electro-acupuncture, which has less side effects and good tolerance. Furthermore, this approach also reduces the dosage and side effects of opioids, such as morphine, and improves the quality of life of patients. We present the following article/case in accordance with the CONSORT Reporting Checklist (available at <http://dx.doi.org/10.21037/apm-19-434>).

Methods

Patient source

The present study was carried out in accordance with the Declaration of Helsinki (as revised in 2013) and the relevant standards and regulations for clinical trials in China. The Ethics Committee approved the present study prior to its implementation (No. 2015-001). All patients provided a signed informed consent. A total of 130 patients with common bone metastases, and long-term persistent pain or recurrent paroxysmal pain, who could be treated with TEAS during hospitalization from January 2015 to December 2017, were enrolled into the present study. Registration number is ChiCTR2000030549 and name of trial register is Chinese Clinical Trial Registry).

Research methods

The randomized control method was adopted (SPSS software randomized grouping) to divided these patients into the following two groups.

TEAS group (n=65): Han's six-lead TEAS machine (HANS-100B) was used for TEAS for 5 days, twice a day.

Acupoint selection: double upper limb: bilateral Hegu + Neiguan/Waiguan (Waiguan was selected for patients with upper limb pain); both lower limbs: Zusanli + Sanyinjiao were selected; Jiaji acupoints on both sides of the target site (on both sides of the spinous process, 0.5 cuns apart). The 2/100 Hz dilatational wave was adopted. The present intensity was appropriate when the patient's maximum tolerance was reached. The range was within 10–15 mA for the upper limb, the range was within 15–30 mA for the lower limb, and the range was 25–40 mA for the Jiaji acupoint area.

Drug control group (n=62): drugs + false TEAS (the selected acupoints were the same with those in the TEAS treatment group, the current was set to 1 mA) was used for the treatment. According to the National Comprehensive Cancer Network (NCCN) 2018 edition of the Guidelines for Adult Cancer Pain, the dosimetric titration and adjustment of opioids, and conversion of equivalent dosage of opioids were carried out. These drugs were continuously administered for 5 days according to the design of the study.

In the present study, TEAS treatment was single-blinded (patient). Since the present study used a single-blinded control method, each patient was 50% likely to enter the control group. Therefore, from the 6th day of the trial, patients with poor efficacy in the two groups were given the corresponding drug treatment or TEAS treatment, according to the patient's preference. Patients in the TEAS group and drug control group were required to fill in the case report form, "A Prospective Clinical Study (XSFHCC-001) on the Observation of the Curative Effect of Electro-Acupuncture on Bone Metastasis Pain in Cancer Patients", before treatment, in order to complete the anxiety survey. The visual analog scale (VAS) scores were assessed at the beginning and end of the trial, and before and after each treatment.

Observation indexes

Pain intensity assessment

VAS score: 0 indicates painless, 10 indicates severe pain, and scores between the two ends part indicate varying degrees of pain.

Degree of anxiety and pain

The Self-Rating Anxiety Scale (SAS) was used to evaluate the patients. The criteria are as follows: (I) no presence or presence for a very short time; (II) presence sometimes; (III) presence most of the time; 4, presence most of the time.

Table 1 VAS scores before and after treatment (mean \pm SD)

Groups	N	Mild	Moderate	Score before first treatment	Score after last treatment	P
TEAS group	62	41	21	3.74 \pm 1.17	1.19 \pm 0.99	<0.01
Drug control group	65	38	27	4.00 \pm 2.26	1.44 \pm 1.02	<0.01
P	–	–	–	0.418	0.182	

VAS, visual analog scale; SD, standard deviation; TEAS, transcutaneous electrical acupoint stimulation.

The curative effect was evaluated according to the pain grading method (VAS score): complete remission (CR), no pain after treatment; partial remission (PR), pain after treatment is significantly milder than that before administration, sleep is basically undisturbed, and the patient can live a normal life; mild remission (MR), the pain after treatment is milder than that before administration, but the patient still feels obvious pain, and sleep is still disturbed; non-remission (NR), there is no relief of pain after treatment, when compared to that before treatment. Effective remission rate = (CR + PR)/case number \times 100%.

Immune indicators

Flow cytometry was used to detect T cells, B cells, CD3⁺CD4⁺ T cells, CD3⁺CD8⁺ T cells and natural killing (NK) cells [D FACSCanto™ II Flow Cytometer (SN: V33947300234)]. A BD lymphocyte subgroup detection kit (batch number: 40902/95982/32954/31833/53789/70258/22607/84752/40732) was used.

Result analysis

Data were statistically analyzed using statistical software SPSS 20.0. All statistical tests were conducted using a one-sided test. The significant level was set at $P \leq 0.05$. Normally distributed measurement data were compared using *t*-test, while non-normally distributed data were compared using Wilcoxon rank-sum test. Count data were compared using Chi-square test.

Results

General data

The differences in age and gender between the two groups were not statistically significant. Furthermore, the differences in disease type and bone metastasis site were also not statistically significant.

VAS scores before and after treatment

All 127 patients had mild-to-moderate bone metastasis pain. The TEAS score was 3.74 \pm 1.17 before the initial treatment and drug control group 4.00 \pm 2.26 before the initial treatment, the difference was not statistically significant. The scores in each group significantly decreased after the last treatment. The pairwise comparison using *t*-test revealed that the difference was statistically significant ($P < 0.01$). After treatment, these scores were significantly lower in the TEAS group than in drug control group (Table 1).

Anxiety degree

In the TEAS group, the SAS score was 50.65 before treatment and 45.77 after treatment, and the difference was statistically significant ($P = 0.001$). The SAS score for the TEAS group was 45.77 after treatment, while the SAS score for the drug control group was 47.78 after treatment, and the difference between these two groups was not statistically significant ($P = 0.160$, Table 2).

Immune indexes

Before treatment, the differences in B cell and CD8 between the two groups were statistically significant, but the differences in the remaining indexes were not statistically significant ($P > 0.05$). After treatment, the differences in B cell and CD8 between the two groups were statistically significant, but the difference in the remaining indexes were not statistically significant (Table 3).

Comparison of pain scores before and after treatment in the TEAS group

In the present study, the VAS score for the TEAS group before and after 10 treatments were analyzed and summarized. The results revealed the following: first,

Table 2 Comparison of anxiety scores of patients before and after treatment (mean \pm SD)

Groups	N	Sleep score before treatment	SAS score before treatment	SAS score after treatment	P
TEAS group	62	9.97 \pm 4.09	50.65 \pm 8.01	45.77 \pm 8.47	<0.01
Drug control group	65	10.00 \pm 5.36	48.37 \pm 10.46	47.78 \pm 7.59	<0.01
P	–	0.970	0.169	0.160	

SD, standard deviation; SAS, Self-Rating Anxiety Scale; TEAS, transcutaneous electrical acupoint stimulation.

Table 3 Comparison of the average number of immune cells in patients before and after treatment (mean \pm SD)

Groups	N	T	B	NK	CD4	CD8	CD4/CD8
Before treatment							
TEAS group	62	725.55 \pm 318.67	162.19 \pm 116.50	216.46 \pm 150.91	420.00 \pm 266.21	283.85 \pm 127.22	1.71 \pm 1.34
Drug control group	65	874.95 \pm 272.49	142.81 \pm 109.51	229.83 \pm 191.29	486.39 \pm 176.76	372.60 \pm 162.27	1.60 \pm 1.03
P		0.005	0.336	0.664	0.102	0.001	0.623
After treatment							
TEAS group	62	727.57 \pm 296.72	172.69 \pm 140.22*	251.45 \pm 143.68	437.71 \pm 246.87	254.44 \pm 123.69*	2.04 \pm 1.35
Drug control group	65	800.64 \pm 282.43	127.32 \pm 105.56	211.92 \pm 164.05	467.81 \pm 180.91	306.59 \pm 128.05	1.81 \pm 1.06
P		0.158	0.041	0.152	0.433	0.021	0.286

*, P<0.05. SD, standard deviation; TEAS, transcutaneous electrical acupoint stimulation.

after each TEAS treatment, the VAS score significantly decreased, when compared with that before treatment, and this increased again at the following day and repeatedly changed, presenting a serrated shape on the chart. Second, the comparison of scores before the first and 10th treatment exhibited a gradually decreasing trend, and the difference was statistically significant. Finally, the comparison of scores after the first and 10th treatment revealed a gradual decreasing trend, but the difference was not statistically significant (*Figure 1*).

Overall efficacy evaluation

In the drug control group, the total effective rate was 100%, in which the cured rate was 24.6% and the improvement rate was 75.4%. In the TEAS group, the total effective rate was 93.5%, in which the cured rate was 24.2% and the improvement rate was 69.4%. However, the difference between these two groups was not statistically significant (*Table 4*).

Discussion

In the present study, the exploration was carried out based on existing research. Focus was given on the aspect of bone metastatic cancer pain, which has special physiological and pathological characteristics, but is difficult to treat in clinic, in order to further alleviate the pain of patients and improve their quality of life.

Transcutaneous electrical nerve stimulation (TENS) is a peripheral stimulation that transmits low-frequency pulse current to the human body through the skin to relieve pain (16). It is different from traditional nerve stimulation in the following aspects: traditional electrical stimulation mainly stimulates motor fibers, while TENS mainly stimulates sensory fibers, and it can stimulate both sensory and motor fibers when the stimulus parameters are changed, or the stimulus reaches the threshold. TEAS has low frequency and high strength, and the electrodes are mostly placed on specific acupoints, which can produce similar effects, such as acupuncture and moxibustion. In clinic, frequency conversion and different current

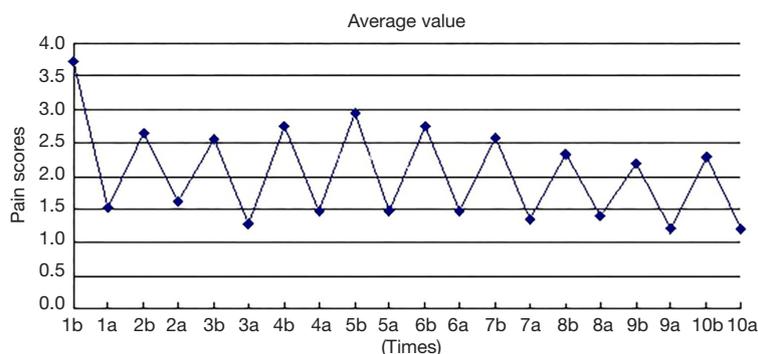


Figure 1 Distribution trend of average value pain scores. After each TEAS treatment, the VAS score significantly decreased, when compared with that before treatment, and this increased again at the following day and repeatedly changed, presenting a serrated shape on the chart. Second, the comparison of scores before the first and 10th treatment exhibited a gradually decreasing trend, and the difference was statistically significant. Finally, the comparison of scores after the first and 10th treatment revealed a gradual decreasing trend, but the difference was not statistically significant. Note: a = after; b = before.

Table 4 Overall efficacy evaluation

Groups	CR	NR	PR	Total
TEAS group	15	4	43	62
Drug control group	16	0	49	65

CR, complete remission; NR, non-remission; PR, partial remission.

intensities are commonly used to make TENS produce a variety of stimuli, causing the central nervous system to secrete enough analgesic substances to achieve a better therapeutic effect.

The present study revealed the following: (I) the pain score for the TEAS group exhibited a serrated shape on the chart before and after treatment, manifesting as a decrease in score after treatment, and after maintaining the analgesic effect for 6 hours, the pain score gradually increased and returned to the similar level before treatment; (II) the analgesic effect of TEAS was significant and persistent, especially at 5 days after treatment, and the VAS score exhibited a downward trend, when compared with that before treatment; (III) subgroup analysis: TEAS alone can relieve pain and has persistence; (IV) the total effective rate in the TEAS group was similar to that in the drug control group. These results reveal that acupuncture and moxibustion, or acupuncture and moxibustion combined with drugs can achieve the same analgesic effect as drugs. The results of the present study further confirm that acupuncture and moxibustion, or TEAS have significant analgesic effects, and that these analgesic effects were persistent. The reason may be the sustained release of

endorphins stimulated by TEAS and the regulation of local inflammatory mediators. This needs to be further explored in combination with experimental research.

In terms of anxiety, the present study revealed the following: (I) the differences in SAS scores before and after treatment in the TEAS group was statistically significant; (II) the difference in SAS score between the TEAS group and drug control group was not statistically significant. These results reveal that acupuncture and moxibustion can alleviate the anxiety of patients with cancer pain, and achieve the same effect as drugs.

In terms of immune indexes, the present study revealed the following: (I) B cells: the difference between the two groups was statistically significant. (II) CD8: since the average value before treatment was higher in the drug control group than in the acupuncture group, the difference between these two groups was statistically significant, which cannot be compared with that after treatment. In order to further clarify the effect of acupuncture and moxibustion on CD8, this was compared before and after treatment in the TEAS group. The results revealed that the difference before and after treatment was not statistically significant. In the drug control group, this exhibited a significant downward trend after treatment. These results reveal that TEAS treatment can prevent the decrease in CD8 caused by drug therapy alone. However, the specific mechanism needs to be further clarified. (III) T, CD4, NK and CD4/CD8: The differences between the TEAS group and drug control group were not statistically significant.

In the present study, although more evidence has been

obtained to support TEAS analgesia, and confirmed its advantages of safety, low incidence of constipation, and ability to maintain the normalization of immune function, various detailed aspects still needs to be improved in the analgesic process. For example, pain must be assessed before the treatment. For patients with mild, moderate and severe pain, different treatment measures should be taken in time. Furthermore, the method of selecting acupoints should be unified as far as possible, and the acupoint selection method based on syndrome differentiation and local acupoints should be mainly applied (17). It is easy to identify the presence of needling sensation in patients with acupuncture or electro acupuncture experience. However, it is difficult to conduct a randomized, double-blinded, controlled trial on acupuncture and moxibustion, or electro-acupuncture in the treatment of cancer pain. It is recommended to use different current intensities as controls.

Conclusions

The analgesic effect of TEAS is significant and persistent. The mechanism may be correlated to the sustained release of endorphins stimulated by TEAS, the regulation of local inflammatory mediators, and the regulation of immune function. TEAS or TEAS combined with drugs can achieve the same analgesic effect as drugs, and can improve a patient's anxiety. Furthermore, TEAS can prevent the decrease in CD8 caused by drug therapy alone.

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Footnote

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[org/10.21037/apm-19-434](http://dx.doi.org/10.21037/apm-19-434)). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. I confirm that I have read the Editorial Policy pages. This study was conducted with approval from the Ethics Committee of Xiaoshan First Hospital Affiliated to Medical College of Hangzhou Normal University (No. 2015-001). This study was conducted in accordance with the declaration of Helsinki (as revised in 2013). Written informed consent was obtained from all participants.

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