Original Research Articles

Transcutaneous Electrical Acupoint Stimulation for the Treatment of Withdrawal Syndrome in Heroin Addicts

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Abstract

Objective. To assess the therapeutic effect of transcutaneous electric acupoint stimulation (TEAS) for the treatment of withdrawal syndrome in heroin addicts.

Methods. A total of 63 male heroin addicts with withdrawal score higher than 20 were recruited in the Detoxification Center of Zhongshan city, Guangdong province, China. They were randomly distributed into two groups: TEAS group (n = 31) received TEAS by using a Han’s acupoint nerve stimulator (HANS) model 200A with two output channels, 2–3 sessions per day, 30 minutes per session for 10 consecutive days. Electrical stimulation of alternating frequencies of 2- and 100- Hz with 3 second each, and with intensity of 10–15 mA was applied on Hegu (LI-4) and Laogong (PC-8) points on one hand, and Neiguan (PC-6) and Waiguan (SJ-5) points on the other forearm via electroconductive skin pads of 4 cm × 4 cm in size. The control group (n = 32) was treated with similar procedure except that the leads of the output of the stimulator was disconnected. Assessments of the severity of the withdrawal syndrome were conducted one day before and on each day during the whole treatment period of 10 days. Buprenorphin of 1 mg per day sublingually was provided to all subjects in the first two days, and then to those with withdrawal score over 20 in the following days.

Results. The TEAS treatment dramatically alleviated the withdrawal syndrome during heroin detoxification. No significant difference was found in withdrawal scores between the two groups at the beginning of the observation. Withdrawal scores showed a more marked drop in TEAS group than the control starting from the second day, and maintained at a lower level for the whole course of treatment. The area under the curve of withdrawal score in TEAS group was only 40% of that in the control (P<0.001, two way repeated measures analysis of variance), and the requirement of buprenorphine was only 10% of that in the control. No adverse effects were observed in either group.

Conclusion. TEAS of 2/100 Hz for 10 days in abrupt abstinence of the heroin addicts resulted in a marked reduction of the withdrawal syndrome as well as a reduced requirement for rescue opioids.

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Key Words. Acupuncture; Electroacupuncture; Transcutaneous Electrical Acupoint Stimulation; Transcutaneous Electric Acupoint Stimulation; Heroin Dependence; Withdrawal Syndrome; Buprenorphine

Introduction

Drug problem is a social issue worldwide. In China, there were dramatic fluctuation in the history of drug abuse in the last two centuries. From 1839 to 1949, it was extremely popular to take opium for nonmedical purposes, which almost disappeared after 1949. The opium or heroin abuse started again since 1990. The number of drug abuser was reported to be about 70,000 in 1990. There was a sharp increase year by year to 2,475,000 in registered abusers in 2013 [1]. The number increased 34 times during the 23 years. If the ratio is 1:5 between the numbers of registered abuser and actual abuser, the actual number of drug abuser will be estimated to be over 10 million, constituting a serious social problem. Of the many kinds of abused drugs in China, opiates, especially heroin, is still the major one. The number of opiate abusers in 2014 is 1,358,000, or 54.9% of all drug abusers [1].

The treatment of heroin addict starts with the detoxification of heroin. Currently, the main drugs used for the detoxification of heroin globally are methadone and buprenorphine [2], with the strategy of replacing heroin with a long acting and highly potent opiate receptor agonist (such as methadone) or partial agonist (such as buprenorphine), which basically meet the patient’s desire for opioid and to diminish the drug-seeking behavior. However, the withdrawal syndrome would appear again quickly and relapse occurs frequently once methadone is discontinued. Therefore, any method intended to detoxify the heroin shall not only aiming to relief the withdrawal syndrome which occurs immediately after heroin discontinuation but also to reduce the dosage of the detoxification drugs, and finally be free from drugs with dependence. Therefore, alternative strategies for detoxification of heroin should be considered with no or minimum dosages of drugs used in replacement therapy in order to reduce relapse rate after detoxification therapy.

Transcutaneous electric acupoint stimulation (TEAS) is a type of therapy which is based on similar mechanisms mediating the therapeutic effects of acupuncture, a medical art since ancient China. When the metal acupuncture needle is penetrated through the skin into the level of muscle and tendon, manipulations of lifting-thrusting and twirling-rotating are applied, and an analgesic effect is produced. Studies have shown that injection of procaine, a local anesthetic, at the acupoint before a needle is inserted can block the analgesic effect, which suggests that the nerve fibers played a decisive role in the transmission of acupuncture signals [3]. It has also been shown that acupuncture analgesia can be reversed by opiate receptor antagonist naloxone, which suggests that this effect is induced by activation of the opiate receptors [4]. In electroacupuncture, pulsatile current is delivered through the handle of the metal needles [5], therefore, the mechanical stimulation is replaced by the electrical stimulation, which produces analgesic effect similar to that of acupuncture. Further research has found that applying pulsatile current to the skin at acupoints through electroconductive skin pads can activate the underneath tissue and induce similar analgesic effect. This is called TEAS. Results from a study in rat have demonstrated that the efficacy and mechanism of analgesic effect induced by TEAS are similar to that induced by electroacupuncture [6]. Electroacupuncture and TEAS are also effective in relieving the withdrawal syndrome in experimental animals with morphine dependence [7]. Clinical trials using Han’s acupoint nerve stimulator (HANS) device have demonstrated that withdrawal syndrome in heroin addicts was significantly diminished [8], and the doses of methadone used in heroin detoxification significantly reduced [9]. However, the results previously obtained from the heroin addict treatment trials did not totally meet the requirements of randomized controlled clinical trials to rule out the potential influence of psychological effects. In this study, a control group was setup by using the same TEAS equipment and the same skin electrodes placed on the same acupoints but with the output leads of the stimulator disconnected. It was intended to see whether the withdrawal syndrome and the dosages of buprenorphine could be reduced in TEAS group as compared with the control group.

Method

Sixty three male drug addicts from Guangdong Zhongshan Detoxification Center were enrolled into this study from June 2010 to September 2010. This study was approved by the Ethics Committee of Peking University (IRB00001052–10066), and was registered in Clinical-Trial.gov (ChiCTR-TRC-10001007).

Patients Selection

Inclusion Criteria

1) 18 to 55 years, male; 2) conformed by criteria of DSM-IV to be opiates dependence with opiates withdrawal syndrome. The Withdrawal Syndrome Scale used in the present study [10] was provided by the Mental Hygiene Center of West China Hospital, Sichuan University, Changdu, China. Subjects with a baseline score of over 20 was required to be recruited in this study. If all the items are scored with full scale, the total score should be 216; 3) positive for opiates test in urine; 4) the interval between last heroin usage and enrollment is less than 36 hours; 5) the patients volunteered to participate in this trial with informed consent form obtained. Patients who do not meet the above criteria should not take part in this trial.
Exclusion Criteria

1) patients with unconsciousness, severe agitation, or severe dehydration; 2) with severe liver or renal insufficiency; 3) with severe infectious disease; 4) with history of severe neurological disease, mental disease, or suicidal attempt; 5) with severe malnutrition or history of HIV infection; 6) with parallel multiple drug dependence (unable to find the main drug of dependence); 7) participated in clinical trials for other therapies in the last 1 month; h) previously experienced acupuncture therapy.

The basic information of the 63 heroin addicts was listed in Table 1.

Randomization and Control

Setup

Patients in treatment group was treated with a HANS model 200A. A device with the same appearance and indicator light was used for patients in control group, except that the leads of output current were disconnected.

Randomization

Residents of Zhongshan city and migrant workers were allocated by cluster randomization. According to previous experience, if the two kinds of subjects reside in one room, physical altercations will occur, therefore, the two kinds of subjects were separated in different rooms, and were allocated to TEAS group and control group by drawing lots. As a result, 32 local subjects were allocated to TEAS group and 31 migrant workers to control group. There was no communication between the two groups.

The basic information of the subjects is listed in Table 1. There was no significant difference between the two groups in age, types of addicted drugs, methods of the drugs abuse (snorting or intravenous injection), total baseline scores of withdrawal syndrome, etc. The only difference was that the history of drug abuse for local subjects was longer than migrant workers (median: 84 months vs 25 months; Mann Whitney test: \( P = 0.002 \)).

Operation of TEAS

Acupoint selection and parameters of the electric stimulation: Hegu (LI-4) and Laogong (PC-8) points on one hand, and Neiguan (PC-6) and Waiguan (SJ-5) points on the other forearm were used. The frequency of stimulation current was 2/100 Hz, that is, alternating frequency shifting between 2 Hz (pulse width 0.6 ms) and 100 Hz (pulse width 0.2 ms), each lasting for 3 seconds. Duration for one session was 30 minutes.

Stimulation Intensity

The default value was set as 10 mA which was 2 times of the sensory threshold (5 mA), and it was adjusted according to the subjective feeling of the patients to make the patients feel comfortable. The actual stimulation intensities were in the range of 7 mA to 15 mA.

Duration of Treatment

The duration of treatment was 10 days consecutively. Patients were treated 3 times a day in the first phase of the treatment (day 1 to day 5), and 2 times a day in the second phase (day 6 to day 10).

Table 1 Baseline information of heroin addicts

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>TEAS</th>
<th>Statistics</th>
<th>( t, X^2 )</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>31</td>
<td>32</td>
<td></td>
<td>( t )</td>
<td>0.7</td>
</tr>
<tr>
<td>Age (Y)</td>
<td>33.5 ± 7.4</td>
<td>34.2 ± 6.5</td>
<td></td>
<td>( X^2 )</td>
<td>0.43</td>
</tr>
<tr>
<td>Other abused drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepan</td>
<td>2</td>
<td>5</td>
<td>( X^2 )</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>7</td>
<td>10</td>
<td>( X^2 )</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>3</td>
<td>6</td>
<td>( X^2 )</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>Ecstasy</td>
<td>5</td>
<td>5</td>
<td>( X^2 )</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Methamphetamine + Caffeine</td>
<td>4</td>
<td>3</td>
<td>( X^2 )</td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td>Ketamine</td>
<td>5</td>
<td>6</td>
<td>( X^2 )</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Methods of drug abuse</td>
<td></td>
<td></td>
<td></td>
<td>( X^2 )</td>
<td>0.13</td>
</tr>
<tr>
<td>i.v.</td>
<td>22</td>
<td>28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Dragon”</td>
<td>9</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of drug abuse (month, M ± Q)</td>
<td>36 (36)</td>
<td>84 (57)</td>
<td>Mann Whitney</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Time from last drug use (h)</td>
<td>27.68 ± 7.01</td>
<td>27.88 ± 6.36</td>
<td>( t )</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>Score of first assessment</td>
<td>51.42 ± 19.09</td>
<td>48.41 ± 17.26</td>
<td>( t )</td>
<td>0.51</td>
<td></td>
</tr>
</tbody>
</table>

Data with normal distribution are presented as mean ± SD; Nonparametric data are presented as median (quantile range)
**Administration of Buprenorphine**

The same dose of buprenorphine was administrated to subjects in both groups to make the withdrawal syndrome tolerable during the study: 1) in the first two days, two tablets of buprenorphine were provided (0.5 mg per tablet, sublingually administered), one in the morning and one in the evening. If the subject was enrolled into the trial in the afternoon, the subject will only receive one tablet in the evening. 2) Buprenorphine will not be given if the subjects did not think it is necessary. 3) one to two additional tablets of buprenorphine can be provided within the same day depending on the severity of withdrawal syndrome and by patient’s request. Other treatments can be provided to the patients with severe symptoms. The degree of discomfort patients experienced, type of drugs received and the dosages were documented timely.

**Method for Scoring in Withdrawal Syndrome Scale**

**Subjective Score**

Degree 0: no symptom; Degree I: subjects reported symptoms upon inquiry; Degree II: subjects reported symptom to be tolerable without additional treatment; Degree III: symptoms intolerable. 2) Objective score (such as pupil size, blood pressure, heart rate, respiration rate, etc.): The grades were classified according to the degree of actual measurement deviated from normal value (Degree 0, I, II, and III); different scores were assigned for different degrees of symptoms.

**Statistical Analysis**

Withdrawal syndrome was determined by the same trained medical doctor according to the Withdrawal Syndrome Scale. The baseline value was measured on the day of hospitalization (day $-$ 1); the whole treatment period was 10 days with two measurements per day (8:00 AM and 19:00 PM), the means were then calculated. Data with normal distribution were presented as mean $\pm$ standard deviation (SD), $t$ test was used for comparison between the two groups, and two ways analysis of variance (ANOVA) showed that there were significant differences on the time factor, treatment-related factors and the interaction of time and treatment factors between the two groups ($P < 0.0001$). Post hoc analysis indicated that there was significant difference on the total scores of withdrawal syndrome from the day 2 to day 10 between the two groups ($P < 0.0001$, see Figure 1).

**Musculoskeletal Pain**

Musculoskeletal pain is one of the most prominent in withdrawal syndromes. According to the nonparametric analysis, the medians and interquartiles of the pain score within 10 days in the control group and TEAS group were calculated, being 3.9 (3.8) and 1.6 (2.0), respectively. The Mann Whitney test indicated that there was a striking difference between the two groups ($P < 0.0001$). The median of musculoskeletal pain of the TEAS group during 10 days was 59% lower than the control group (see Table 2).

**Results**

All 63 subjects completed the study in this clinical trial. Only one subject in the control group required one session of intravenous fluid infusion for vomiting and diarrhea.

**Craving**

The strong craving for drugs during the detoxification period is one of the major causes for relapse to drug. The nonparametric analysis of the scale data indicated that the median of score for drug desire of the control group and TEAS group were 0.65(0.55) and 0.25(0.38), respectively, within the 10 days. Mann Whitney test indicated that there was very significant difference between the two groups ($P < 0.0001$). The craving score of TEAS.
group within 10 days was 62% lower than the control group (see Table 2).

### Psychiatric Symptoms: Anxiety, Insomnia, and Agitation

#### Anxiety

Results shown in Figure 2 indicated a significant difference on the temporal factor, treatment-related factors and the interaction of time and treatment factors between the two groups \( P < 0.0001 \). When measured as AUC, the anxiety of the TEAS group was 60% lower than the control group.

#### Insomnia

Insomnia usually goes with anxiety. However, the anxiety score was relatively stable, but the degree of insomnia

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### Table 2 Changes in withdrawal syndrome

<table>
<thead>
<tr>
<th>No.</th>
<th>Item</th>
<th>Control</th>
<th>TEAS</th>
<th>( P ) value</th>
<th>Statistic Method</th>
<th>Percentage of Scores in Both Groups (Mean or Median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Musculoskeletal pain</td>
<td>3.9(3.8)</td>
<td>1.6(2.0)</td>
<td>0.0001</td>
<td>Mann Whitney</td>
<td>100:41</td>
</tr>
<tr>
<td>2</td>
<td>Craving</td>
<td>0.65(0.55)</td>
<td>0.25(0.38)</td>
<td>0.0001</td>
<td>Mann Whitney</td>
<td>100:38</td>
</tr>
<tr>
<td>3</td>
<td>Anxiety</td>
<td>1.76 ± 0.30</td>
<td>0.65 ± 0.47</td>
<td>0.0001</td>
<td>RM ANOVA</td>
<td>100:37</td>
</tr>
<tr>
<td>4</td>
<td>Insomnia</td>
<td>6.2(2.6)</td>
<td>1.6(2.0)</td>
<td>0.0001</td>
<td>Mann Whitney</td>
<td>100:26</td>
</tr>
<tr>
<td>5</td>
<td>Agitation</td>
<td>1.4(2.0)</td>
<td>0.4(0.75)</td>
<td>0.0001</td>
<td>Mann Whitney</td>
<td>100:29</td>
</tr>
<tr>
<td>6</td>
<td>Sleepiness</td>
<td>3.2(1.8)</td>
<td>1.0(0.8)</td>
<td>0.0001</td>
<td>Mann Whitney</td>
<td>100:31</td>
</tr>
<tr>
<td>7</td>
<td>Yawn</td>
<td>2.0±0.3</td>
<td>0.6 ± 0.6</td>
<td>0.0023</td>
<td>RM ANOVA</td>
<td>100:30</td>
</tr>
<tr>
<td>8</td>
<td>Abdominal pain and diarrhea</td>
<td>2.0(2.7)</td>
<td>0.6(1.1)</td>
<td>0.0006</td>
<td>Mann Whitney</td>
<td>100:30</td>
</tr>
<tr>
<td>9</td>
<td>Nausea and vomiting</td>
<td>0.8(2.2)</td>
<td>0.5(0.6)</td>
<td>0.0062</td>
<td>Mann Whitney</td>
<td>100:63</td>
</tr>
<tr>
<td>10</td>
<td>Anorexia</td>
<td>1.7(2.1)</td>
<td>0.9(1.1)</td>
<td>0.0024</td>
<td>Mann Whitney</td>
<td>100:53</td>
</tr>
<tr>
<td>11</td>
<td>Running nose</td>
<td>0.4(1.3)</td>
<td>0.2(0.5)</td>
<td>0.0001</td>
<td>Mann Whitney</td>
<td>100:50</td>
</tr>
<tr>
<td>12</td>
<td>Lacrimation</td>
<td>1.7(1.2)</td>
<td>0.5(0.4)</td>
<td>0.0001</td>
<td>Mann Whitney</td>
<td>100:29</td>
</tr>
<tr>
<td>13</td>
<td>Sweat</td>
<td>1.4(1.4)</td>
<td>0.2(0.3)</td>
<td>0.0001</td>
<td>Mann Whitney</td>
<td>100:14</td>
</tr>
<tr>
<td>14</td>
<td>Shivering</td>
<td>3.2±0.9</td>
<td>1.3 ± 1.3</td>
<td>0.0001</td>
<td>RM ANOVA</td>
<td>100:41</td>
</tr>
<tr>
<td>15</td>
<td>Score of pupil expansion</td>
<td>5.1 ± 1.6</td>
<td>3.5 ± 1.9</td>
<td>0.0004</td>
<td>t</td>
<td>100:69</td>
</tr>
<tr>
<td>16</td>
<td>Score of spontaneous ejaculation</td>
<td>5.0 (7.5)</td>
<td>2.5 (6.9)</td>
<td>0.0538</td>
<td>Mann–Whitney</td>
<td>100:50</td>
</tr>
<tr>
<td>17</td>
<td>Body weight</td>
<td>54.3±0.4</td>
<td>54.8±0.3</td>
<td>0.7026</td>
<td>RM ANOVA</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Heart rate</td>
<td>68.0±3.1</td>
<td>66.9±1.8</td>
<td>0.4572</td>
<td>RM ANOVA</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Score of blood pressure</td>
<td>0(0.4)</td>
<td>0(0.2)</td>
<td>0.4302</td>
<td>Fisher’s exact</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Hyperpnea</td>
<td>0(0.2)</td>
<td>0(0)</td>
<td>0.0596</td>
<td>Fisher’s exact</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Limbs flexion</td>
<td>0.15(0.6)</td>
<td>0(0.15)</td>
<td>0.2101</td>
<td>Fisher’s exact</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Muscle tremor</td>
<td>0(0.15)</td>
<td>0(0)</td>
<td>0.387</td>
<td>Fisher’s exact</td>
<td></td>
</tr>
</tbody>
</table>

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**Figure 2** Changes of the anxiety score during the 10-day TEAS treatment. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
fluctuated dramatically each day. The median of insomnia values within 10 days for each subject was calculated to be 6.2 (2.6) and 1.6 (2.0) for the control and TEAS group, respectively. Mann Whitney test indicated a very significant difference between the two groups ($P < 0.0001$). The severity of insomnia of the TEAS group within 10 days was 74% lower than the control group (see Table 2).

**Agitation**

The median of agitation symptom of TEAS group and control group were 0.4 (0.75) and 1.4 (2.0), respectively. Mann Whitney test indicated a very significant difference between the two groups ($P < 0.0001$). The agitation symptom of the TEAS group within 10 days was 71% lower than the control group (see Table 2).

**Gastrointestinal Symptoms: Abdominal Pain, Diarrhea, Nausea, Vomiting, and Anorexia**

Gastrointestinal symptoms constituted important part of the withdrawal syndrome, including abdominal pain, diarrhea, nausea, vomiting, and anorexia. The mean values of gastrointestinal symptoms within 10 days were listed in Table 2. Nonparametric test revealed significant improvement of the TEAS group over the control group ($P < 0.01$), with the mean values of abdominal pain, diarrhea and/or nausea, and vomiting and/or anorexia decreased for 70%, 37%, and 47%, respectively.

**Sleepiness and Yawn**

Sleepiness and yawn are typical symptoms of the opium withdrawal syndrome. The values of sleepiness did not show a pattern of normal distribution. The severity of sleepiness of the TEAS group within 10 days was 69% lower than the control group ($P < 0.0001$). The frequency of yawn of the TEAS group within 10 days was 70% lower than the control group ($P = 0.0023$) (see Table 2 and Fig. 3).

**Catarrh-Like Symptoms: Running Nose, Lacrimation, Sweat, and Shivering**

Opium withdrawal syndrome includes some catarrh-like symptoms such as running nose, lacrimation, sweat, and shivering. These symptoms were decreased in the TEAS group. The first three symptoms were analyzed by Mann Whitney test, while shivering was analyzed by RM ANOVA. The results revealed that there was significant difference between the two groups ($P < 0.0001$). All symptoms of patients in the TEAS group were over 50% lower than the control group (see Table 2).

**Autonomic Nervous System Function: Heart Rate, Pupil Size, and Spontaneous Ejaculation**

**Heart Rate**

The heart rate in all subjects decreased on the second day after enrolment which increased gradually thereafter, and returned to the original level on the day 10 (see Figure 4). RM ANOVA revealed that changes of heart rate with time were statistically significant in both groups ($P < 0.0001$), but there was no significant difference between the two groups.

**Score of Pupil Expansion**

The mean values of control group and TEAS group within 10 days were 5.1 ± 1.6 and 3.5 ± 1.9, respectively. The dilated pupil returned toward normal size more quickly in the TEAS group ($P < 0.001$).

**Spontaneous Ejaculation**

According to the Withdrawal Syndrome Scale, the incidences of spontaneous ejaculation (0, 1-, 2-, 4-) were scored as 0, 5, 10, 15. The total score of each subject within 10 days was calculated for the two groups. The median and the interquartile range was 5.0 (7.5) in the
control group and 2.5 (6.9) in the TEAS group. Non-parametric test (Mann–Whitney U test) revealed that score of ejaculation of the TEAS was trending lower than that of the control group, but the difference was not statistically significant ($P = 0.0538$).

**Change in Body Weight**

RM ANOVA revealed that the body weights of both groups increased slightly but significantly within 10 days ($P < 0.0001$). However, there was no significant difference between the two groups (see Table 2).

**Blood Pressure, Respiration, Limb Flexion, and Muscle Tremor**

As shown in Table 2, there was no significant difference in blood pressure, respiration, limb flexion, and muscle tremor between the two groups.

**Dosages of Buprenorphine (Number of Tablets) Administered in the Two Groups**

Medications were offered to comfort the patients when necessary. The results obtained within 10 days were shown in Table 3. The Fisher’s exact test revealed that there was no significant difference in the baseline dosage of buprenorphine between the two groups, but the dosage of buprenorphine requested by the subjects in the TEAS group was significantly less than the control group ($P < 0.0001$).

Every subject received follow-up assessment for the “actual feeling” of acupoint stimulation under the skin pads after the end of the trial. The following question was asked: “Did you feel obvious sense of stimulation under the electrodes,” and the optional answer includes yes, not sure and no. All subjects in the TEAS group answered “Yes”. Seventeen subjects in the control group answered “Yes,” eight “not sure,” and six “no.” No statistically significant difference was found between the two groups, suggesting that the design of the blinding in this trial was satisfactory.

**Discussion**

**Advantages of TEAS Treatment for Opium Addicts**

Many potentially addictive drugs can be obtained illegally, and new drugs emerged quickly one after another, including stimulants and hallucinogens. However, with regard to the hazard to the human life and refractoriness after addiction, heroin remains the top one among these drugs. Maintenance therapy with methadone, an opium receptor agonist was first introduced to treat the opiate withdrawal syndrome in early 1970s. Partial agonists of opium receptor, such as buprenorphine, were introduced in 2000. This was followed by a combination therapy of buprenorphine and opiate antagonist naloxone (buprenorphine: naloxone = 4:1), resulting in comparable success than buprenorphine alone. Recent development has shown a trend from lifelong medication to dosage tapering of methadone or buprenorphine, aiming at a final drug free status [11]. For example, the therapy designed by Donovan et al. includes four phases: 1) detoxification: 5 to 6 days; 2) treatment in hospital (mainly with clonidine): 4 weeks; 3) treatment outside of hospital: 5 months; 4) maintenance period: variable. Donovan et al. investigated the actual records from 2008 to 2009 from a rehabilitation center at King County, Seattle. Eight hundred fifty two patients with opium addiction were admitted for detoxification, only 85 patients (10%) actually completed the detoxification step, 12 patients received treatment outside hospital, and only one patient had completed the therapy finally, with a successful rate of 1.2% (1/852). It showed vividly that while the treatment protocol was designed reasonably, the successful rate can be extremely low. The efficacy of the above protocol was fully dependent on exogenous drugs, without taking into consideration of the potential of activating the endogenous opioid system of the opiate addicts. The work in our laboratory since 1975 revealed that electroacupuncture with 100 Hz can activate the gene expression of dynorphin in the central nervous system of rats, and improvement of the production and release of dynorphin in the spinal cord markedly inhibit the withdrawal syndrome in rats with morphine dependence [12]. Conversely, electroacupuncture with 2 Hz can activate the gene expression of enkephalin and beta-endorphin in the brain of rats, and facilitates the production and release of enkephalin and beta-endorphin, thereby decreases the conditioned place preference (CPP) induced by morphine[13]. A combined application of 2 Hz and 100 Hz (2 Hz alternating with 100 Hz, each lasing for 3 seconds) not only can inhibit the withdrawal syndrome in rats with morphine dependence but also inhibits the CPP induced by morphine [14]. Moreover, these results were preliminarily confirmed in humans [14–16].

**Reproducibility of Efficacy of TEAS Treatment on the Withdrawal Syndrome**

The 22 items in the questionnaire can be grouped into 10 units which are listed in Table 2. Significant inhibition of withdrawal syndrome in the TEAS group was observed in 16 items in seven units (including pain, desire for drug, psychentonia, sleepy and yawn, gastrointestinal symptoms, catarrh symptoms, and vegetative

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**Table 3** Buprenorphine dosage (tablets) consumed in each group

<table>
<thead>
<tr>
<th>Group</th>
<th>$n$</th>
<th>Given</th>
<th>Requested</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOCK</td>
<td>32</td>
<td>76</td>
<td>29</td>
</tr>
<tr>
<td>TEAS</td>
<td>31</td>
<td>73</td>
<td>3*</td>
</tr>
</tbody>
</table>

*$P < 0.0001$, Fisher’s exact test.
nerve dysfunction), with a total inhibition rate of 60% within 10 days. This is consistent with previous reports from our lab [15,16] and from other labs using the HANS [17,18]. However, reproducibility was not achieved in six items from three units. The potential reasons for the inconsistency in achieving the therapeutic effects for various symptoms in the present and previous studies are discussed as follows:

**Regarding the Change of Body Weight**

In a previous report [8], the patients with heroin addiction received treatment with HANS 30 minutes QD during detoxification. The mean body weight in the HANS group increased from 50 kg to 55 kg (P < 0.01) while the body weight in the control group decreased. In the present study the mean body weights in the control group and TEAS group were 55.0 kg and 55.5 kg, respectively, at the beginning of the trial, and the body weight in both groups increased only 0.5 kg at the end of the trial (P < 0.0001). Unlike those seen in the previous study, there was no additional body weight gain in TEAS group compared with the control group in the present study. In depth survey revealed that although the incidence of nausea, vomiting, abdominal pain, and diarrhea decreased significantly in the treatment group which would predict an increase in appetite, there was no increase in food intake, due to a fixed ration provided every day during the trial.

**Regarding the Change of Heart Rate**

In a previous report [16], the heart rate of the patients with heroin addiction who received treatment with HANS during detoxification was more than 100 beats per minute (bpm). The heart rate decreased to below 90 bpm in the treatment group after treatment for four days. In the present study, the initial heart rate before the treatment was only 75 bpm which was within the normal physiological range and, therefore, would not expect a further decrease after treatment. For the same reason, there was no significant difference being revealed in blood pressure and heart rate between the two groups.

**Regarding the Severity of Heroin Withdrawal Syndrome**

Since the severity of withdrawal syndrome observed in patients in 2010 was significantly less than that in 1995 and 1996, we hypothesized that lower doses of heroin were consumed due to a decrease in purity of heroin available in the market. A survey on the purity of heroin on black market was made in Beijing area by Forensic Medical Identification Center of Beijing Public Security Bureau [19]. The report shows that the purity of heroin was 40–70% in 2005, while the purity of 223 samples collected in 2008 was only 10–40%. A total of 13 samples collected from Guangzhou Public Security Bureau in 2008 and 13 samples from Zhongshan Public Security Bureau in 2010 were tested by the Identification Center of Guangzhong public security system. The average purities were 42% in 2008 samples and 20% in 2010 samples. The results agree with the data obtained from Beijing Area that the purity of heroin in 2010 was approximately half of that in 1998. It is not surprising to see a less severe withdrawal syndrome in the present study.

**Regarding the Parameters of TEAS Treatment**

Previous studies indicated that 100 Hz TEAS was more effective than 2 Hz for the treatment of withdrawal syndrome [7,12]; while the efficacy of 2 Hz TEAS was better than 100 Hz for the inhibition of craving for opioids [14]. An alternating 2/100 Hz stimulation can achieve good efficacy on both aspects [14]. Therefore, a dense-disperse mode of 2 Hz and 100 Hz (3 second each) was used in this trial. Concerning acupoints selection, a set of four acupoints and a set of eight acupoints have been used and compared in our previous studies in the treatment of heroin withdrawal syndrome. Comparisons have been made in efficacy and no significant differences were found between the two protocols. Therefore, a set of four acupoints was used in the present trial. Regarding the number of sessions per day, we used to give one session for 30 minutes daily to treat heroin withdrawal syndrome in 1995 and 1996 [16] with certain success. However, results from our animal research indicated that more sessions per day of electroacupuncture stimulation (30 min per session) within a certain range (up to four sessions per day) will enhance the efficacy of detoxification and increase the after-effect [17]. Therefore, three sessions daily in the first 5 days and two sessions daily in the last 5 days were given in this clinical trial. As shown in Figures 1–3, the scores of withdrawal syndrome decreased by half from the 2nd day which was better than the results obtained in a previous study. Therefore, three sessions per day seems to be more effective than one session per day, at least in the first five days of the therapy.

**Regarding the Combined Use of Buprenorphine and Methadone**

One mg of buprenorphine daily was provided in the first two days in this trial to alleviate the withdrawal syndrome. This dose was consistent with that reported by Li XD [18], but much lower than that used in the US [11]. On top of this baseline dosage, one can ask for more when needed. Comparison of the rescue dose of buprenorphine requested by the patients revealed that the TEAS group requested much less buprenorphine than that in the control group. This is in line with our previous report showing that TEAS can reduce the dose of methadone and increase the retention time of methadone maintenance [9]. Since the
dropout rate of patients in methadone maintenance program was reported to be as high as 63% in China [20], if TEAS can prolong the retention of methadone maintenance, it may well contribute to the prevention of heroin relapse. This is also supported by a recent paper by Meade et al., showing that opioid addicts treated with TEAS are less likely to use drugs after their discharge from the hospital and reported to have greater improvements in pain interference and physical health [21].

Limitation of this Trial

Randomized setup of control and treatment group is one of the most important methodological requirements in clinical trials. The ideal arrangement is that the eligible patients were randomized to the control group and the TEAS group. However for reasons already mentioned above, local people and migrant workers were located in two separated rooms. The most important difference between the two populations is that the history of drug abuse is shorter in the migrant workers. As shown in Table 1, the medians are 36 months and 84 months, respectively, with a ratio of 1:2.33. According to the draw lots, local subjects received TEAS treatment. Since the history of drug abuse in the TEAS group is longer than that in the control group, it would be logical to infer that the severity of withdrawal syndrome and the resistance to TEAS treatment should be greater in the TEAS group. However, as shown in Table 1, the mean total scores of actual withdrawal syndrome were similar in the two groups and the efficacy of TEAS was obvious in the treatment group, suggesting that drug addicts with a history of as long as 7 years were still reactive to TEAS treatment.

Conclusion

TEAS with the HANS device was applied on four acupoints located on the upper limbs, 30 minutes per session and two to three sessions per day for 10 days. The withdrawal syndrome in the TEAS group was 60% lower than that in the control group, and the residual syndrome in the TEAS group was 80% lower than that in the control group. Furthermore, the dosage of the rescue drug buprenorphine requested by the patients was only 10% in the TEAS group compared with that of the control. Results from this study strongly suggest that the treatment seems to be safe and effective. The TEAS therapy is warranted to be validated in larger multicenter clinical trials.

Acknowledgments

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