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CLINICAL TRIAL REPORT

Treatment of Moderate-to-Severe Pain in Hepatocellular Carcinoma with Transcutaneous Electrical Acupoint Stimulation: A Randomized Controlled Trial

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Objective: Moderate-to-severe pain is the most common clinical symptom in patients with hepatocellular carcinoma (HCC).This trial aimed to analyze the clinical efficacy of Transcutaneous electrical acupoint stimulation (TEAS) in patients of HCC with severe pain and provide a reliable reference for optimizing the clinical diagnostic and therapeutic strategies of HCC.

Methods: A total of 104 eligible patients were randomly allocated to experimental and control groups in a ratio of 1:1.The treatment was administered for 1 week continuously. Patients in both groups were followed up 1 week after the end of the treatment.The primary outcome measure was the Numerical Rating Scale (NRS) score, whereas the secondary outcome measures included Brief Pain Inventory BPI-Q3, Q4, Q5 scores, analgesic dose, frequency of opioid-induced gastrointestinal side effects, Karnofsky Performance Status (KPS), Quality of Life Scale - Liver Cancer (QOL-LC), and Brief Fatigue Inventory (BFI) scores.

Results: The NRS scores of experimental group was significantly lower after treatment and at the follow-up than baseline (average $P<0.01$), there were also statistical differences between the groups at the above time points (average $P<0.01$). BPI-Q3, -Q4, and -Q5 scores in the experimental group were decreased after treatment when compared with those before treatment (average $P<0.01$). Furthermore, there were significant improvements of gastrointestinal side effects, KPS, QOL-LC and BPI in the experimental group after treatment, and the above results were statistically significant compared to the control group.

Conclusion: 7-day TEAS treatment can significantly enhance the analgesic effect and maintain for the following week, also reduce the incidence of gastrointestinal side effects caused by opioids, and improve the quality of life of patients with moderate-to-severe HCC-related pain, which has reliable safety and certain clinical promotion value.

Keywords: hepatocellular carcinoma pain, transcutaneous electrical acupoint stimulation, cancer pain, randomized controlled trial

Introduction

Hepatocellular carcinoma (HCC) is defined as a malignant tumor originating from hepatocytes and represents the most common subtype of primary liver cancer (PLC), with approximately 75–85% of PLC cases being attributed to HCC worldwide. The relative 5-year survival rate of patients with HCC is only 18%.[1] 90% of HCC patients experience pain symptoms due to overgrowth of liver tumors, their invasion or infiltration of surrounding tissues, and their suppressive effects on the nociceptors of adjacent organs, most of these patients experience moderate to severe pain.[2,3] Persistent pain

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seriously affects the quality of life of patients, and can even accelerate the progression of HCC, increase the risk of death, and bring heavy economic pressure and mental burden to their families.[4]

The three-step analgesic regimen formulated by the World Health Organization (WHO) is most widely used for treating moderate-to-severe pain in HCC in clinical settings. In particular, patients with moderate pain are treated with weak opioid drugs, mainly codeine (Step 2), whereas those with severe pain are treated with strong opioid drugs, mainly morphine and oxycodone (Step 3).[5] Long-term use of opioids may cause nausea, vomiting, constipation, lethargy, and respiratory depression, seriously affecting the quality of life of patients.[6,7] Moreover, patients may get addicted to opioids to some extent and experience withdrawal symptoms after discontinuing them. Therefore, opioids have limited therapeutic efficacy and may affect the physical and mental health of patients.[8,9] In most cases, HCC results from the progression of hepatitis or cirrhosis. Increasing the dose of opioids can further impair liver function in patients with HCC and lead to hepatic encephalopathy.[2] Altogether, opioids have limited potential in the treatment of moderate-to-severe pain in HCC. Therefore, developing safer and more effective treatment strategies for cancer-related pain is necessary.

Transcutaneous electrical acupoint stimulation (TEAS), a modernized treatment method for acupuncture, offers unique advantages in the treatment of cancer-related pain. A case study reported that the visual analogue scale (VAS) scores of patients with advanced pancreatic cancer were significantly decreased after 2/100-Hz TEAS was used to continuously stimulate local Ashi points and the ipsilateral Yanglingquan (GB34) and Zusanli (ST36) points for 1 week.[10] Similarly, a small-sample study on patients with cancer-related pain (irrespective of tumor category) suggested a significant decrease in VAS scores after 30 days of TEAS treatment.[11] This randomized controlled trial aimed to assess the efficacy of TEAS, so that to provide more effective and less side effect clinical treatment strategy to alleviate moderate-to-severe pain in HCC.

Methods

Trial Design

This study was designed as a single-center, prospective, randomized controlled trial. Ethical approval was received from the Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine Committee (No.2021–021). This trial was registered with the China Clinical Trial Center (ChiCTR2100044615) and strictly adhered to the guidelines established by the Consolidated Standards of Reporting Trials (CONSORT) and Helsinki declaration. All patients voluntarily signed an informed consent form.

Setting and Participants

Patients were recruited from the Department of Oncology, Yueyang Hospital of Integrated Medicine, Shanghai University of Traditional Chinese Medicine, from November 2021 to November 2023. The inclusion criteria were as follows: (1) Patients who met the diagnostic criteria for HCC; (2) Patients aged ≥50 and ≤80 years, with no limitations on their sex; (3) NRS score of ≥4 in the past 24h; (4) Patients with Child–Pugh grade A or B; (5) Patients with an expected survival period of > 3 months; (6) Patients with clear consciousness and capable of estimating their pain and quality of life; (7) Patients who agreed to sign the informed consent form. The exclusion criteria were as follows: (1) Patients with other physical or pathological pain; (2) Patients who had undergone tumor resection within the past 3–6 months; (3) Patients with severe complications such as persistent ascites, abdominal infections, gastrointestinal bleeding, liver failure, and abdominal hemorrhage; (4) Patients with severe acute or chronic organ diseases or mental disorders; (5) Patients with localized skin injuries; (6) Patients who had previously undergone TEAS treatment; (7) Patients scheduled for surgery within 14 days.

Randomization and Allocation Concealment

In this single-blind trial, a simple and randomized method was used for grouping, in which patients who met the inclusion criteria were randomly allocated to experimental or control groups in a ratio of 1:1. Random allocation sequences were generated by statisticians using the SPSS (version 26.0) software. According to the standard operating procedure (SOP), the sequences were placed in sequentially numbered, opaque, sealed envelopes by an assistant who was

not involved in patient recruitment, treatment, and evaluation. When the patients were ready for participation, physicians with TEAS experience opened the envelopes according to the order of patient visits to allocate the patients into groups for subsequent treatment. Unblinded personnel included physicians with TEAS experience and a research assistant in charge of managing randomization modules. The remaining personnel were blinded.

Interventions

This trial was conducted in the oncology department of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine. Patients with HCC in both groups were treated with radiotherapy, chemotherapy, interventional therapy, or other conventional treatments according to the NCCN Clinical Practice Guidelines for Hepatobiliary Cancer.[12] TEAS was performed by acupuncturists with at least 3 years of clinical experience to ensure a complete understanding of the treatment protocol.

Experimental Group

The acupoints used for TEAS included bilateral Hegu (LI4), Neiguan (PC6), Zusanli (ST36), Taichong (LR3), Ganshu (BL18), Geshu (BL17), Qimen (LR14), and Zhangmen (LR13), with the names and locations of acupoints being marked according to the national standard (GB/T 12346–2021) of People's Republic of China (PRC) formulated in 2021. The skin was locally disinfected before treatment. A 3*3-cm square electrode slice was attached to the relevant acupoints and connected with the HANS Acupuncture Point Nerve Stimulator (model number: JS-502-A; Wuxi Shenping Xintai Medical Technology Co., Ltd., Jiangsu, China). Subsequently, the power switch was turned on for stimulation. Patients in the experimental group were treated twice a day at different time points, with joint intervention being realized through two low-frequency nerve regulators. At 10:00 a.m., the positive pole of the electrode slice of one instrument was connected to the bilateral Hegu acupoint, and the negative pole was connected to the bilateral Taichong acupoint. The positive pole of the electrode slice of another instrument was connected to the bilateral Geshu acupoint, and the negative pole was connected to the bilateral Ganshu acupoint. Furthermore, at 04:00 p.m., the positive pole of the electrode slice of one instrument was connected to the bilateral Neiguan acupoint, and the negative pole was connected to the bilateral Zusanli acupoint. The positive pole of the electrode slice of another instrument was connected to the bilateral Qimen acupoint, and the negative pole was connected to the bilateral Zhangmen acupoint. The entire treatment lasted 1 week. Parameters for TEAS were set as follows: density wave of 2/100 Hz, stimulation time of 30 minutes, and current intensity of 5–10mA (which makes the patient feel evident but tolerable electrical stimulation). The location of the acupoints is shown in Figures 1 and 2

Control Group

In the control group, the current intensity was set to 0.5 mA for weak electrical stimulation. Other parameters, including the selection of acupoints, operation steps, and frequency and period of intervention, were the same as those in the experimental group.

Patients who developed persistent pain symptom during the observation period were treated according to the WHO three-step analgesic regimen. In particular, weak opioids, mainly codeine and tramadol, were used to treat moderate pain, whereas strong opioids such as morphine, oxycodone, and fentanyl were used to treat severe pain.

Sample Estimation

The sample size for this trial was estimated using the two-proportional comparison method. On estimating the sample size based on the reviewed literature resources, the mean NRS score was found to decrease by 0.051 in the experimental group and increase by 0.585 in the control group. The combined standard deviation was 1.06. The sample size was determined using the following equation, with α value of 0.05 (two-sided) and β value of 0.1 (90% power).

$$n = 2\left(Z_{\alpha/2}+Z_{\beta}\right)^2\times\rho^2/(\mu_2-\mu_1)^2$$

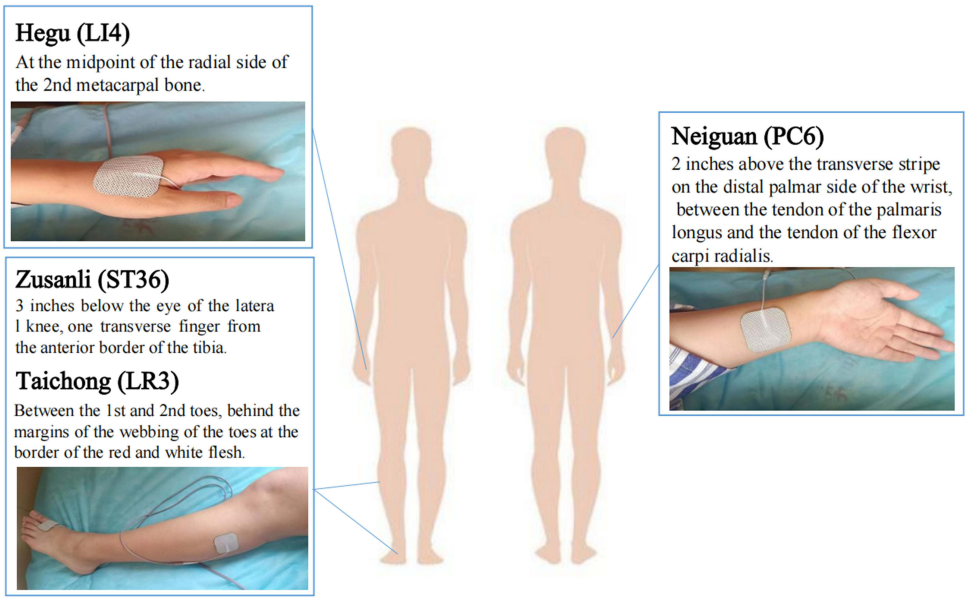

Figure 1 Location of Acupoints: from left to right: Hegu (LI4), Zusanli (ST36), Taichong (LR3), Neiguan (PC6).

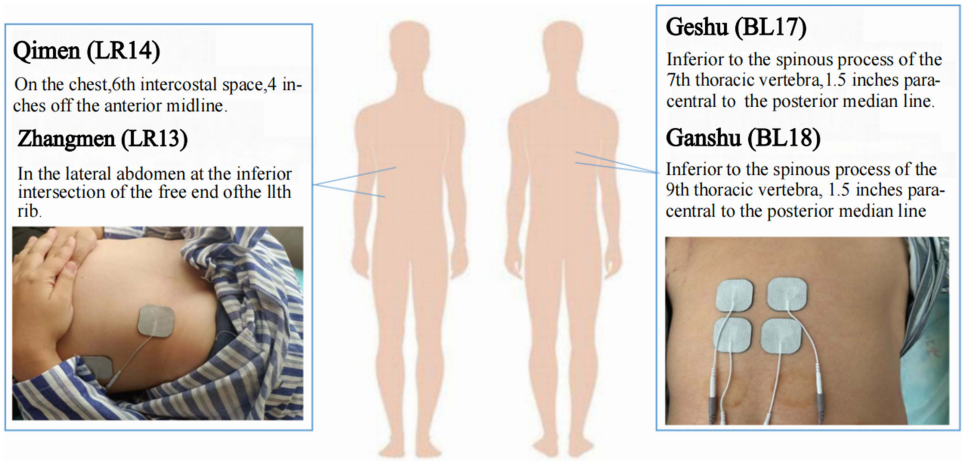

Figure 2 Location of Acupoints: from left to right: Qimen (LR14), Zhangmen (LR13), Geshu (BL17), Ganshu (BL18).

According to the results of sample size estimation, approximately 45 participants were required in each group. The sample size was increased to 52 cases considering a 15% drop-out rate, and a total of 104 patients were eventually included.

Baseline Assessment

Baseline information included demographic characteristics (sex, age, height, and weight), disease duration, tumor stage, Child–Pugh grade, NRS pain scores, dosage of analgesics used, and quality of life scores.

Primary Outcome

The Numerical Rating Scale (NRS)[13] was used to measure pain severity as the primary outcome measure. It assesses the level of pain on a scale of 0 to 10, with a score of 0 indicating no pain, a score of 1–3 indicating mild pain, a score of 4–6 indicating moderate pain, and a score of 7–10 indicating severe pain. Pain severity was respectively assessed at 3 time points: baseline, the end of the treatment (T1), and 1 week after the treatment (T2).

Secondary Outcomes

(1) BPI-Q3, -Q4, and -Q5 scores: BPI was used to assess the intensity of cancer-related pain.[14] The scale uses a digital scale from 0 to 10 to rate each item, with a score of 0 indicating no pain and a score of 10 indicating an unimaginable degree of pain. The third, fourth, and fifth questions of the BPI questionnaire correspond to the most severe degree, the least severe degree, and the average degree of pain in patients within 24 hours. BPI scores were evaluated at 2 time points: baseline, the end of the treatment (T1).

(2) Dosage of analgesics: The dosage of different types of analgesics was converted according to the equivalent dosage conversion method of the NCCN Guideline for Adult Cancer Pain[15] to obtain and evaluate the total dosage used during treatment.

(3) Frequency of opioid-induced gastrointestinal side effects: The gastrointestinal side effects of opioids include nausea, vomiting, abdominal distension, constipation, diarrhea, and dry mouth. These symptoms were evaluated at 3 time points: baseline, the end of the treatment (T1), and 1 week after the treatment (T2).

(4) Comprehensive assessment of quality of life: The Karnofsky Performance Status Scale (KPS),[16] Quality of Life Scale - Liver Cancer (QOL-LC),[17] and Brief Fatigue Inventory (BFI) scale[18] were used for assessing the quality of life of patients at 2 time points: baseline, the end of the treatment (T1).

Statistical Analysis

All data were analyzed using the SPSS (version 26.0) software.A full analysis set was used for the intention-to-treat analysis, and missing data were processed using imputation method and replaced with the last observation carried forward (LOCF) data sets.

Measurement data were evaluated for normality and homogeneity of variance. Qualified measurement data were expressed as the mean (SD), whereas unqualified measurement data were expressed as the median (Q1, Q3). Measurement data that conformed to a normal distribution and had homogeneity of variance were compared using the independent-sample *t*-test and paired *t*-test between and within groups, respectively. Furthermore, a non-parametric test was used for analyzing unqualified technical data. Count data were denoted by the number of cases and compared using the chi-square test, with *P*-values of <0.05 indicating statistically significant differences. Repeated measurement data that conformed to a normal distribution and had homogeneity of variance were compared using ANOVA, whereas data that did not conform to a normal distribution and had heterogeneity of variance were analyzed using generalized estimating equations(GEEs). Groups and measurement time served as the main effects for comparison. The interaction effect between groups and measurement time was in the form of a pairwise comparison to compare differences between groups. Eventually, the Bonferroni test was used to correct the α value in all pairwise comparisons.

Results

Participants

A total of 114 patients with HCC with moderate-to-severe pain were initially evaluated, and 104 eligible patients, including 69 men and 39 women, were eventually included in this trial.

Of the 104 patients, 94 (90.4%) patients, including 63 men (67.0%) and 31 women (33.0%), completed the trial. The mean age of patients in experimental group was 58.00 (53.25, 65.00) and in control group was 58.50 (53.00, 65.00) years, respectively.

A total of 10 (9.6%) patients withdrew from the trial owing to various reasons (3 patients in the experimental group withdrew owing to COVID-19 infection and disease progression, 2 patients dropped out of treatment midway through the study, 4 patients in the control group refused to continue owing to poor outcomes, and 1 patient withdrew owing to disease progression). Table 1 shows the baseline demographic and clinical characteristics of the included patients.The number of patients who withdrew and the reasons for withdrawal are shown in the flowchart in Figure 3.

Table 1 Baseline Demographic and Clinical Characteristics of the Included Patients

Characteristic	Experimental Group (n=52)	Control Group (n=52)	P
Gender, No.(%)			
Male	35.00(67.30%)	34.00(65.40%)	0.836[a]
Female	17.00(32.70%)	18.00(34.60%)	
Age, median(Q_1,Q_3), years	58.00(53.25, 65.00)	58.50(53.00, 65.00)	0.715[b]
Height, median(Q_1,Q_3), cm	168.00(160.50, 172.00)	168.00(158.50, 171.75)	0.691[b]
Weight, median(Q_1,Q_3), kg	60.00(50.25, 66.50)	55.00(50.25, 64.25)	0.580[b]
Duration of disease median(Q_1,Q_3), months	6.00(2.00, 12.00)	2.50(1.00, 8.00)	0.052[b]
NRS score, median(Q_1,Q_3)	6.50(5.00, 7.00)	6.00(5.00, 7.00)	0.635[b]
Dose of opioid drugs median(Q_1,Q_3), mg	0.00(0.00, 15.00)	0.00(0.00, 19.5)	0.885
Quality of life, median(Q_1, Q_3)	104.00(83.00, 118.00)	94.50(83.25, 106.75)	0.198[b]
Child Pugh Grade, No.(%)			
A	26.00(50.00%)	31.00(59.60%)	0.325[a]
B	26.00(50.00%)	21.00(40.40%)	
Tumor Stage, No.(%)			
I	2.00(3.80%)	4.00(7.70%)	0.639[a]
II	6.00(11.50%)	9.00(17.30%)	
III	22.00(42.30%)	18.00(34.60%)	
IV	22.00(42.30%)	21.00(40.40%)	

Notes: Data are presented as number of patients (%) or median (Q1,Q3). [a]Analyzed using chi-squared test. [b]Analyzed using Mann–Whitney-*U* test.
Abbreviation: NRS, numerical rating scale.

Primary Outcome

The results of GEE-based comparison of NRS scores between the experimental and control groups are demonstrated in Table 2 and Figure 4. The NRS scores of the two groups were almost similar at baseline. However, the scores of the

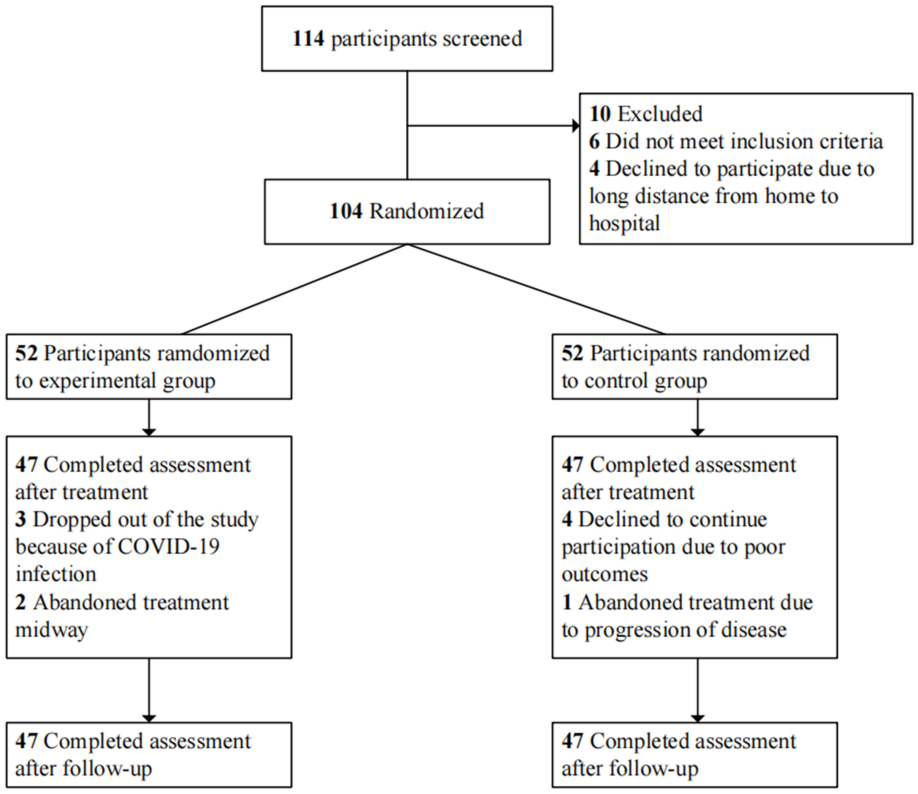

Figure 3 Flowchart of this study.

Table 2 Comparison of NRS Scores Based on Generalized Estimated Equation Analysis

Variables	Baseline	T1	T2	P[a]
Experimental Group (n=52)	6.50 (5.00, 7.00)	5.00 (3.00, 6.00)[bc]	5.00 (2.25, 6.00)[bc]	<0.001
Control Group (n=52)	6.00 (5.00, 7.00)	6.00 (5.00, 8.00)	6.00 (5.00, 7.00)	

Notes: Data are presented as median (Q1,Q3). [a]GEE was applied for repeated measures. [b]Compared with the Control group, the difference was statistically significant. [c]Compared with Baseline within the same group, the difference was statistically significant.
Abbreviations: NRS, numerical rating scale; T1, the end of the treatment; T2, 1 week after the treatment.

experimental group decreased significantly after treatment compared with those before treatment (intra-group difference: −1.75 [95% CI, −2.59 to −0.91]). This trend continued until the follow-up (intra-group difference: −1.81 [95% CI, −2.71 to −0.91]). On the contrary, the NRS scores of the control group did not change significantly after treatment (intra-group difference: 0.25 [95% CI, −0.22 to 0.72]) and at the follow-up (intra-group difference: −0.10 [95% CI to −0.64, 0.45]).

Regarding inter-group comparisons, the NRS scores of the experimental group were significantly lower than those of the control group after treatment (inter-group time difference: 1.96 [95% CI, 1.26 to 2.67]). Moreover, the NRS scores of the experimental group were significantly lower than those of the control group at the follow-up (inter-group time difference: 1.60 [95% CI, 0.87 to 2.33]).

Secondary Outcomes

BPI-Q3, -Q4, and -Q5 Scores

Table 3 demonstrates the results of intra-group comparison of BPI scores. The BPI scores of the two groups were almost similar at baseline. Differences between the scores of the two groups after treatment are shown in Table 4. In particular, the average BPI-Q3 scores of the experimental group decreased by 1.44 (95% CI, −1.93 to −0.95; $P<0.001$). The BPI-Q3 scores of the experimental group were significantly lower than those of the control group after treatment, with a decrease of 1.25 (95% CI, 0.60 to 1.89; $P=0.001$). The average BPI-Q4 scores of the experimental group decreased by 0.92 (95% CI, −1.45 to −0.39; $P=0.002$). No significant differences were observed in BPI-Q4 scores between the experimental and control groups after treatment, with a decrease of only 0.77 (95% CI, 0.07 to 1.46; $P = 0.071$). The average BPI-Q5 scores of the experimental group decreased by 1.98 (95% CI, −2.41 to −1.55; $P<0.001$). The BPI-Q5 scores of the experimental group were significantly lower than those of the control group after treatment, with a decrease of 1.92 (95% CI, 0.34 to 2.51; $P< 0.001$).

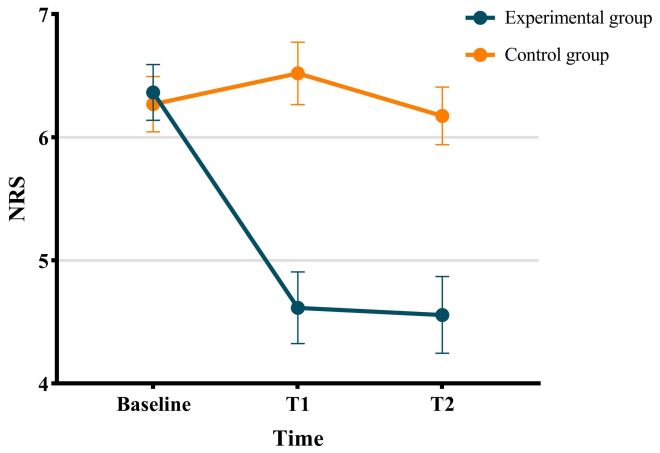

Figure 4 Trend chart of changes in NRS scores.

Table 3 Comparison of the Treatment Effects in the Experimental Group and Control Group

Variables	Time	Experimental Group (n=52)	Control Group (n=52)
BPI Q3	Baseline	6.00 (5.25, 8.00)	6.50 (5.00, 8.00)
	T1	5.00 (3.25, 6.00)[b]	6.00 (5.25, 8.00)
	Difference, 95% CI	−1.44 (−1.93,-0.95)	−0.19 (−0.61, 0.22)
	P[a]	<0.001	0.228
BPI Q4	Baseline	2.00 (1.00, 5.00)	4.00 (2.00, 5.00)
	T1	1.00 (0.00, 4.00)[b]	3.00 (2.00, 5.00)
	Difference, 95% CI	−0.92 (−1.45,-0.39)	−0.15 (−0.59, 0.28)
	P[a]	0.002	0.517
BPI Q5	Baseline	6.00 (5.00, 7.00)	5.00 (4.25, 6.00)
	T1	3.00 (2.00, 4.75)[b]	5.00 (4.25, 6.00)
	Difference, 95% CI	−1.98 (−2.41,-1.55)	−0.06 (−0.43, 0.31)
	P[a]	<0.001	0.501

Notes: Data are presented as median (Q1,Q3). [a]Analyzed using Mann–Whitney-*U* test. [b]Compared with Baseline within the same group, the difference was statistically significant.
Abbreviations: BPI, brief pain inventory; T1, the end of the treatment.

Table 4 Comparison of the Treatment Effects Between 2 Groups and Baseline

Variables	Experimental Group (n=52)	Control Group (n=52)	Difference (95% CI)	P[a]
BPI Q3	−1.00 (−3.00, 0.00)[b]	0.00 (−1.00, 0.00)	1.25 (0.60, 1.89)	0.001
BPI Q4	−1.00 (−3.00, 0.00)	0.00 (−1.00, 0.00)	0.77 (0.07, 1.46)	0.071
BPI Q5	−2.00 (−3.00, 0.00)[b]	0.00 (−1.00, 0.25)	1.92 (1.34, 2.51)	<0.001

Notes: Data are presented as median (Q1,Q3). The difference data shown in the table are all differences obtained by subtracting the baseline values from the post-intervention values. [a]Analyzed using Mann–Whitney-*U* test.[b]Compared with the Control group, the difference was statistically significant.
Abbreviation: BPI, brief pain inventory.

Dosage of Analgesics

Table 5 demonstrates the differences in the dosage of analgesics used during the treatment period between the experimental and control groups. No significant differences were observed between the two groups (43.24 [95% CI, −36.38 to 122.36], $P = 0.720$).

Incidence of Opioid-Induced Gastrointestinal Side Effects

The incidence of gastrointestinal side effects was not significantly different between the two groups at baseline. After treatment, the incidence of all gastrointestinal side effects was low in the experimental group. In particular, the incidence of abdominal distension (P=0.018), nausea (P=0.027), and vomiting (P=0.001) was significantly lower in the experimental group than in the control group. At the follow-up, the incidence of all gastrointestinal side effects was low in the experimental group. The incidence of nausea (P=0.031) and dry mouth (P=0.028) was significantly lower in the experimental group than in the control group (Table 6 shows the specific incidence of gastrointestinal side effects in the two groups).

Table 5 The Dosage of Analgesics Comparison Between Two Groups

	Experimental Group (n=52)	Control Group (n=52)	Z[a]	P[b]
Analgesic dose, mg	0.00 (0.00, 84.38)	0.00 (0.00, 198.75)	−1.344	0.179

Notes: Data are presented as median (Q1,Q3). [a]Z-value obtained by comparing the same time point between the two groups. [b]Analyzed using Mann–Whitney-*U* test.

Table 6 The Specific Incidence of Gastrointestinal Side Effects

Variables	Experimental Group (n=52)			Control Group (n=52)		
	Baseline	T1	T2	Baseline	T1	T2
Constipation n(%)	11(21.2)	8(15.4)[b]	7(13.5)[b]	17(32.7)	6(16.5)[b]	10(19.2)
Diarrhea n(%)	7(13.5)	3(5.8)[b]	3(5.8)[b]	4(7.7)	6(11.5)	4(7.7)
Abdominal distention n(%)	35(67.3)	22(42.3)[ab]	37(71.2)	35(67.3)	24(65.4)[b]	37(71.2)
Dry mouth n(%)	8(15.4)	5(9.6)[b]	6(11.5)[ab]	13(25.0)	12(23.1)[b]	15(28.8)
Nausea n(%)	19(36.5)	15(28.8)[ab]	19(36.5)[a]	25(48.1)	26(50.0)	30(57.7)
Vomiting n(%)	11(21.2)	2(3.8)[ab]	4(7.7)[b]	6(11.5)	14(17.5)	10(19.2)

Notes: Data are presented as number of patients (%). All the data were analyzed using chi-squared test. [a]Compared with the Control group, the difference was statistically significant. [b]Compared with Baseline within the same group, the difference was statistically significant.
Abbreviations: T1, the end of the treatment; T2, 1 week after the treatment.

Comprehensive Assessment of Quality of Life

Table 7 depicts the differences in KPS, QOL-LC, and BFI scores within groups, and Table 8 depicts the differences in the three scores between groups. The average KPS scores of the experimental group increased by 2.12 after treatment (95% CI, 0.62 to 3.61; *P*=0.008). The KPS scores of the experimental group were significantly higher than those of the control group after treatment, with an increase of −2.50 (95% CI, −4.76 to −0.24; *P*=0.048). Furthermore, the average QOL-LC

Table 7 Comparison of the Comprehensive Quality of Life in the Experimental Group and Control Group

Variables	Time	Experimental Group (n=52)	Control Group (n=52)
KPS	Baseline	70.00 (70.00, 80.00)	80.00 (70.00, 80.00)
	T1	80.00 (70.00, 80.00)[b]	80.00 (70.00, 80.00)
	Difference, 95% CI	2.12 (0.62, 3.61)	−0.38 (−2.04, 1.27)
	P[a]	0.008	0.687
QOL-LC	Baseline	104.00 (83.00, 118.00)	94.50 (83.25, 106.75)
	T1	115.00 (98.00, 126.00)[b]	95.00 (81.50, 106.75)
	Difference, 95% CI	11.50 (7.90, 15.10)	0.12 (−4.04, 4.27)
	P[a]	<0.001	0.682
BFI	Baseline	51.00 (2.75, 60.75)	45.50 (0.00, 61.75)
	T1	38.00 (2.75, 45.00)[b]	45.50 (0.00, 60.00)
	Difference, 95% CI	−7.50 (−9.49,-5.51)	1.13 (−2.76, 5.03)
	P[a]	<0.001	0.474

Notes: Data are presented as median (Q1,Q3). [a]Analyzed using Mann–Whitney-*U* test. [b]Compared with the same group, the difference was statistically significant.
Abbreviations: KPS, Karnofsky performance status scale; QOL-LC, quality of life-liver cancer; BFI, brief fatigue inventory; T1, the end of the treatment.

Table 8 Comparison of the Comprehensive Quality of Life Between 2 Groups and Baseline

Variables	Experimental Group (n=52)	Control Group (n=52)	Difference (95% CI)	P[a]
KPS	0.00 (0.00, 0.00)[b]	0.00 (0.00, 0.00)	−2.50 (−4.76,-0.24)	0.048
QOL-LC	10.50 (0.25, 21.75)[b]	0.00 (−9.75, 5.75)	−11.38 (−17.03,-5.74)	<0.001
BFI	−6.50 (−14.00, 0.00)[b]	0.00 (−2.00, 0.00)	8.63 (3.61, 13.45)	<0.001

Notes: Data are presented as median (Q1,Q3). The difference data shown in the table are all differences obtained by subtracting the baseline values from the post-intervention values. [a]Analyzed using Mann–Whitney-*U* test. [b]Compared with the Control group, the difference was statistically significant.
Abbreviations: KPS, Karnofsky performance status scale; QOL-LC, quality of life-liver cancer; BFI, brief fatigue inventory; T1, the end of the treatment.

scores of the experimental group increased by 11.50 after treatment (95% CI, 7.90 to 15.10; $P < 0.001$). The QOL-LC scores of the experimental group were significantly higher than those of the control group after treatment, with an increase of −11.38 (95% CI, −17.03 to −5.74; $P < 0.001$). The average BFI scores of the experimental group decreased by 7.50 after treatment (95% CI, −9.49 to −5.51; $P<0.001$). The BFI scores of the experimental group were significantly lower than those of the control group after treatment, with a decrease of 8.63 (95% CI, 3.61 to 13.45; $P < 0.001$).

Discussion

This randomized controlled trial is the first to assess the efficacy of TEAS in the treatment of moderate-to-severe pain in HCC, with high patient acceptance and strong operability. TEAS replaces the traditional acupuncture needles with painless electrodes that are applied to the surface of the patient's skin where the acupoints are located, which can not only maintain the stimulating characteristics of traditional acupuncture and moxibustion, and also overcome some shortcomings of these traditional therapies. Moreover, the control group of this experiment placed square electrode patches on the same acupoints as the experimental group, but the current intensity was set to 0.5mA. Patients only had a weak sensation, but did not produce any biological effects. This electrical stimulation design using low-intensity current as a placebo had been proven scientific and reduced the risk of blinding, ensuring the smooth progress of the trial.[19,20]

We consider that the pathogenesis of pain in patients with HCC is associated with deficiency and excess, the actual treatment should involve acupoints that are convenient for regulating qi, moistening the liver, activating blood circulation to dissipate blood stasis, unblocking meridians, and alleviating pain. The acupoints used to alleviate pain symptoms in routine clinical practice include Hegu (LI4), Neiguan (PC6), and Zusanli (ST36). In this trial, these common acupoints were used in combination with other acupoints, including LR3, BL18, BL17, LR14, and LR13, which have been demonstrated to relieve liver cancer-related pain.[21,22] After one week of TEAS intervention, the NRS score, BPI-Q3 and BPI-Q5 scores of the experimental group at various time points were significantly lower than those of the control group, indicating that TEAS significantly alleviated the overall pain symptoms of HCC patients, especially reducing the most severe and average pain level within 24 hours, achieving a good analgesic effect.Related study[23] have confirmed that 5mA TEAS can activate C-fibers in the local skin of the pain source. On the one hand, it can reduce the release of inflammatory factors and alleviate pain through the dorsal root reflex mechanism. On the other hand, it may also produce analgesic effects by activating the diffuse noxious inhibitory controls.

Notably, patients with HCC with moderate-to-severe pain who use opioids are more likely to have gastrointestinal side effects owing to gastrointestinal dysfunction. Previous studies have demonstrated that TEAS can improve gastrointestinal dysfunction during postoperative recovery.[24] In this trial, TEAS significantly alleviated abdominal distension, nausea, vomiting, and dry mouth in patients with moderate-to-severe HCC-related pain, with the overall incidence of gastrointestinal side effects being significantly low in the experimental group. Moreover, the dosage of analgesics used by patients was not significantly different between the experimental and control groups, which may be attributed to the addiction to and dependence on opioids owing to their long-term use as a means of pain control.[25] In the case of sudden drug withdrawal, patients may experience various withdrawal symptoms such as diarrhea, abnormal thermoregulation, hyperalgesia, and subjective anxiety. Therefore, it is difficult for them to reduce the dosage of opioids in a short time[26.] Furthermore, some patients included in this trial did not use opioids during TEAS treatment because of their side effects. Altogether, individual differences in the dosage of analgesics were observed, leading to a relatively scattered data distribution. Therefore, we did not observe significant differences in the dosage of analgesics between the two groups.

Long-term cancer-related pain not only increases the risk of developing psychological symptoms such as depression, fear, anxiety, anger, and excessive worry but also seriously affects daily activities, social functions, and sleep quality, thereby leading to a decline in the quality of life of patients.[27] In this trial, the KPS and QOL-LC scores of the experimental group were higher than those of the control group, whereas the BFI scores of the experimental group were significantly lower than those of the control group. These findings suggest that TEAS may alleviate cancer-related pain symptoms in patients with HCC, thereby improving their overall health and quality of life.

Limitations

(1) Owing to the COVID-19 pandemic, the overall observation period of this trial was short. Therefore, future studies should include a longer observation period for accurate assessment of the long-term efficacy of TEAS in the treatment of moderate-to-severe pain in HCC.
(2) This trial had a single-center, prospective, randomized controlled design. Given that the short-term use of TEAS can alleviate HCC-related pain, future studies should include patients from multiple centers to examine differences in the analgesic effects of TEAS in a larger population.
(3) In-depth research, serological detection of inflammatory factors and endogenous painful substances such as endorphins should be increased to provide a more powerful scientific basis for TEAS analgesia.

Conclusions

7-day TEAS treatment can significantly enhance the analgesic effect and maintain for the following week, also reduce the incidence of gastrointestinal side effects caused by opioids, and improve the quality of life of patients with moderate-to-severe HCC-related pain, which has reliable safety and certain clinical promotion value.

Data Sharing Statement

We all agree to share individual deidentified participant data. The data used to support the findings of this study are available from the corresponding author (Yan Huang) upon reasonable request in five years.

Consent for Publication

All the authors agreed to publish this article.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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