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Clinical Study

Clinical observation of the effects of moxibustion with seed-sized moxa cone plus opioid drugs on cancer pain and immune function

麦粒灸联合阿片类药物对癌痛及免疫功能影响的临床观察

Bao Guan-ai (鲍关爱)[1], Gong Li-yan (龚黎燕)[1], Du Wei-bin (杜伟斌)[2], Zhang Bo (张波)[1]
1 Zhejiang Cancer Hospital, Hangzhou 310022, China
2 Jiangnan Hospital Affiliated to Zhejiang Chinese Medical University, Hangzhou 311201, China

Abstract
Objective: To observe the clinical efficacy of moxibustion with seed-sized moxa cone plus opioid drugs for moderate-to-severe cancer pain, and the effect on immune function in patients with cancer pain.
Methods: A total of 80 patients with moderate-to-severe cancer pain were randomized into an observation group and a control group by the random number table method, with 40 cases in each group. Both groups were treated with opioid drugs for analgesia according to the standardized management principles for cancer pain. In addition, the observation group was given moxibustion with seed-sized moxa cone. The treatment was performed once a day, continuous 5-day treatment with a 2-day interval constituted a treatment course, and a total of 2 courses were performed. The score of numerical rating scale (NRS) and 24 h equivalent morphine consumption was compared between the two groups before treatment, after 1 treatment course and after 2 courses of treatment. The immune functions were compared between the two groups before and after 2 courses of treatment.
Results: During the treatment, there were 3 dropouts in the control group, and 2 dropouts in the observation group. Before the treatment, there were no significant differences in the NRS score and 24 h equivalent morphine consumption between the two groups (both $P>0.05$). The NRS scores of both two groups were quite stable during the whole treatment period, and there was no significant difference in the intra-group comparison after treatment (both $P>0.05$), and there was no significant difference between the two groups at the same time point (both $P>0.05$). In the control group, the 24 h equivalent morphine consumption showed an increasing trend. The dosage after 1 treatment course and 2 courses of treatment was statistically different from that before treatment in the control group (both $P<0.01$). There was no significant change in the mean 24 h equivalent morphine consumption in the observation group compared with that before treatment (both $P>0.05$). After 2 courses of treatment, the 24 h equivalent morphine consumption in the observation group was significantly lower than that in the control group at the same time point ($P<0.05$). Before treatment, there was no significant difference in the levels of T lymphocyte subsets ($CD3^+$, $CD4^+$ and $CD4^+/CD8^+$) between the two groups (all $P>0.05$). After treatment, the levels of T lymphocyte subsets ($CD3^+$, $CD4^+$ and $CD4^+/CD8^+$) in the control group were lower than those before treatment (all $P<0.05$), while the levels in the observation group were higher than those before treatment, and the levels of $CD3^+$ and $CD4^+$ were significantly different from those before treatment (both $P<0.05$). After treatment, the levels of T lymphocyte subsets ($CD3^+$, $CD4^+$ and $CD4^+/CD8^+$) of the observation group were significantly higher than those of the control group at the same time point (all $P<0.05$).
Conclusion: Moxibustion with seed-sized moxa cone can reduce the dosage of opioid drugs used in patients with moderate-to-severe cancer pain and improve their immune functions.
Keywords: Moxibustion Therapy; Direct Moxibustion; Moxa Cone Moxibustion; Moxibustion with Seed-sized Moxa Cone; Neoplasms; Pain; Pain Measurement; T-lymphocyte Subsets

【摘要】目的：观察麦粒灸联合阿片类药物治疗中重度癌痛的临床疗效及其对癌痛患者免疫功能的影响。**方法：**共纳入中重度癌痛患者80例，采用随机数字表法分为观察组和对照组，每组40例。两组均根据癌痛规范化管理原则，规律使用阿片类药物镇痛。观察组在此基础上加用麦粒灸，每日1次，连续治疗5 d后休息2 d为一个疗程，共治疗2个疗程。于治疗前、治疗1个及2个疗程后比较两组患者的疼痛数字量表(NRS)评分及24 h等效吗啡量；于治疗前及治疗2个疗程后评估两组患者的免疫功能。**结果：**治疗过程中对照组脱落3例，观察组脱落2例。治疗前，两

Author: Bao Guan-ai, M.M., physician of traditional Chinese medicine.
E-mail: doctorbga@126.com

组NRS评分及24 h等效吗啡量均均无统计学差异(均P＞0.05)。两组的NRS分值在整个治疗过程中均较稳定，与治疗前相比均无统计学差异(均P＞0.05)，两组同期比较也无统计学差异(均P＞0.05)；对照组24 h等效吗啡量呈递增趋势，治疗1个及2个疗程后用量与治疗前均具有统计学差异(均P＜0.01)；而观察组的24 h等效吗啡量均值未见明显变化，与治疗前比较均无统计学差异(均P＞0.05)；治疗2个疗程后，观察组24 h等效吗啡量明显低于同期对照组，差异有统计学意义(P＜0.05)。治疗前，两组的T淋巴细胞亚群水平($CD3^+$、$CD4^+$及$CD4^+/CD8^+$)均无统计学差异(均P＞0.05)；治疗后，对照组的T淋巴细胞亚群水平($CD3^+$、$CD4^+$及$CD4^+/CD8^+$)较治疗前降低(均P＜0.05)，而观察组较治疗前略有升高，但仅$CD3^+$和$CD4^+$与本组治疗前有统计学差异(均P＜0.05)，观察组治疗后T淋巴细胞亚群水平($CD3^+$、$CD4^+$及$CD4^+/CD8^+$)明显高于同期对照组(均P＜0.05)。**结论**：麦粒灸可以减少中重度癌痛患者的阿片类药物使用量，提高患者的免疫功能。

【关键词】灸法；直接灸；艾炷灸；麦粒灸疗法；肿瘤；疼痛；疼痛测评；T淋巴细胞亚群

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In recent years, the incidence of malignant tumors has increased year by year, seriously endangering human life. With continuous medical progress, the life of cancer patients has been prolonged, but the complications of tumor still seriously affect the quality of life (QOL) of the patients. Among them, cancer pain (especially moderate-to-severe cancer pain) has gradually become one of the main factors affecting the QOL of cancer patients. Forty percent of early-stage and mid-stage cancer patients and 90% of advanced cancer patients may experience moderate or severe pain[1], and the incidence of pain in patients with advanced cancer is 60% to 80%, and 1/3 of the patients have severe pain[2]. Related studies suggest that cancer pain also has a certain inhibitory effect on the immune function of cancer patients[3-5]. We applied moxibustion with seed-sized moxa cone plus opioid drugs in the treatment of moderate-to-severe cancer pain, and observed the effects on pain and immune-related indicators.

1 Clinical Materials

1.1 Diagnostic criteria

Those who met the diagnostic criteria of National Comprehensive Cancer Network (NCCN) guideline, diagnosed by pathology and/or cytology, or confirmed by imaging combined with specific tumor markers, and accompanied by cancer-related pain.

1.2 Inclusion criteria

Those who met the diagnostic criteria, with a clear site of pain, and were already using opioids to treat cancer pain; aged 18-75 years old; expected survival >3 months; clear consciousness with stable vital signs; Karnofsky (KPS) score ≥60 points; no intellectual and mental disorders; normal language expressiveness; able to judge his/her own situation; able to cooperate with researchers to complete relevant assessments; patients and their families fully aware of the study process, and signed informed consent.

1.3 Exclusion criteria

Those with mental illness or severe cognitive impairment; women during pregnancy; combined with heart, lung, liver or kidney dysfunction; allergic to opioids; patients with other immune-related diseases that affected relevant immune indicators; had skin lesions around the acupoint; those with sensory neuropathy, decreased or loss of the sense to warmth; those who participated in other clinical trials that affected the outcome assessment of this trial.

1.4 Elimination and shedding criteria

Those dropped out during the trial; those presenting with severe adverse reactions, complications, or deterioration of the disease; unable to continue the clinical observation; with poor compliance; those had other analgesics prescribed by other doctors without permission.

1.5 Statistical methods

All data were statistically analyzed by the SPSS version 18.0 statistical software. The measurement data were first tested for normality, and those in normal distribution were processed by *t*-test. If data did not meet the normal distribution, non-parametric test was applied. Chi-square test was applied to the comparison of counting data. P<0.05 was considered to indicate statistical significance.

1.6 General data

A total of 80 patients with cancer pain were enrolled from the Inpatient Department of Zhejiang Cancer Hospital between December 2016 and June 2018. The 80 random numbers generated by SPSS version 18.0 statistical software were made into random distribution cards at a 1:1 ratio and then sealed in envelopes. The patients were divided into an observation group and a control group according to the random distribution cards, with 40 cases in each group. During the treatment, there were 3 dropouts in the control group, and 2 dropouts in the observation group. There were no significant differences in gender, age, height, weight, expected survival and primary lesion between the two groups (all P>0.05), (Table 1 and Table 2).

Table 1. Comparison of gender, age, height, weight and expected survival between the two groups

Group	*n*	Gender (case)		Average age ($\bar{x}\pm s$, year)	Average height ($\bar{x}\pm s$, cm)	Average weight ($\bar{x}\pm s$, kg)	Average expected survival ($\bar{x}\pm s$, month)
		Male	Female				
Observation	38	19	19	58.1±7.9	163.9±9.5	53.1±6.8	7.0±2.7
Control	37	20	17	58.7±9.9	162.9±8.1	52.2±5.1	7.8±2.9

Table 2. Comparison of primary lesion between the two groups (case)

Primary lesion	Observation group (*n*=38)	Control group (*n*=37)
Pulmonary malignant tumor	18	15
Malignant breast tumor	5	4
Malignant tumor of the head and neck	3	3
Gastric malignant tumor	3	4
Malignant ovarian tumors	2	2
Large bowel malignancies	4	4
Pancreatic malignant tumor	1	3
Cervical malignancy	2	2

2 Treatment Methods

2.1 Observation group

2.1.1 Analgesic

Patients were treated with opioid analgesics regularly according to the standardized management principles for cancer pain.

2.1.2 Moxibustion with seed-sized moxa cone

Acupoints: Bilateral Zusanli (ST 36), Sanyinjiao (SP 6), Pishu (BL 20), Ganshu (BL 18) and Shenshu (BL 23).

Moxibustion order: The patient first took a prone position, holding the head with both hands. The physician applied moxibustion to bilateral Pishu (BL 20), Ganshu (BL 18) and Shenshu (BL 23). Then the patient took a supine position, and the physician applied moxibustion to bilateral Zusanli (ST 36) and Sanyinjiao (SP 6).

Methods: Kneaded the moxa floss and tightly twisted it into seed-sized moxa cone. First, applied vaseline as the adhesive on the acupoint skin with a sterile cotton swab, then put the moxa cone on the acupoint and ignited the top of it with incense thread (flicked the ashes of the incense thread before touching the moxa cone so as to prevent the ashes from falling and burning the patient's skin). When the moxa cone burned to 3/5-4/5, and the patient also claimed obvious burning heat, the physician immediately put the remaining moxa cone into a beaker with water using tweezers. This was counted as one cone, and 9 cones were performed successively at each acupoint for each time of moxibustion. Finally, the ashes and vaseline were wiped away from the acupoints with a sterile cotton ball.

Treatment course: Once a day, 5 times a week, then 2 d for rest, which constituted a treatment course, and a total of 2 courses were performed.

2.2 Control group

Patients in the control group received only the same analgesic medications as those in the observation group.

If there was an outbreak of pain during the trial, patients in either group could be given a rescue dosage of short-acting opioids according to the actual situation.

3 Observation of Results

3.1 Observation items

3.1.1 Pain evaluation

The numerical rating scale (NRS) was scored before treatment, after 1 treatment course and after 2 courses of treatment respectively. The average pain intensity during a day was evaluated in both groups.

3.1.2 The 24 h equivalent morphine consumption

The 24 h equivalent morphine consumption was evaluated before treatment, after 1 treatment course and after 2 courses of treatment in both groups.

3.1.3 Immune function items

Five milliliter of fasting peripheral venous blood was collected before treatment and after 2 courses of treatment. The levels of T lymphocyte subsets ($CD3^+$, $CD4^+$, $CD4^+/CD8^+$) of the two groups were measured respectively by flow cytometry.

3.2 Results

3.2.1 Pain assessment and 24 h equivalent morphine consumption

There was no significant difference in the NRS score between the two groups before treatment ($P>0.05$). After 1 week and 2 weeks of treatment, the NRS scores of both groups were stable, and there were no significant differences in the intra-group comparison and between the two groups (all $P>0.05$). There was no significant difference in 24 h equivalent morphine consumption between the two groups before treatment ($P>0.05$). During the treatment, the 24 h equivalent morphine consumption of the control group showed an increasing trend. The dosage after 1 treatment course and 2 courses of treatment was statistically different from that before treatment (both $P<0.01$) in the control group. No significant change was

observed in the 24 h equivalent morphine consumption of the observation group during the treatment, and there was no statistical significance in the intra-group comparison after 1 treatment course and 2 courses of treatment (both $P>0.05$). After 2 courses of treatment, the 24 h equivalent morphine consumption of the observation group was significantly lower than that of the control group at the same time point ($P<0.05$), (Table 3).

3.2.2 Immune function items

There was no significant difference in $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ between the two groups before treatment (all $P>0.05$). After 2 courses of treatment, the $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ levels of the control group were lower than those before treatment, and the intra-group comparisons were statistically significant (all $P<0.01$). However, the $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ levels of the observation group were higher than those before treatment, and the $CD3^+$ and $CD4^+$ levels were statistically different from those before treatment (both $P<0.05$). And the levels of T lymphocyte subsets ($CD3^+$, $CD4^+$, $CD4^+/CD8^+$) of the observation group were significantly higher than those of the control group at the same time point ($P<0.05$ or $P<0.01$), (Table 4).

Table 3. Comparison of the NRS score and 24 h equivalent morphine consumption between the two groups ($\bar{x}$ ±s)

Group	n	NRS score (point)			24 h equivalent morphine consumption (mg)		
		Before treatment	1-week treatment	2-week treatment	Before treatment	1-week treatment	2-week treatment
Observation	38	0.8±0.80	0.8±0.6	0.8±0.5	50.0±21.1	50.0±21.1	50.0±21.1[2)]
Control	37	0.8±0.80	0.8±0.6	0.8±0.4	51.0±22.3	58.0±15.5[1)]	66.0±9.7[1)]

Note: Compared with the same group before treatment, 1) $P<0.01$; compared with the control group at the same time point, 2) $P<0.05$

Table 4. Comparison of immune function items between the two groups before and after intervention ($\bar{x}$ ±s)

Group	n	Time	$CD3^+$ (%)	$CD4^+$ (%)	$CD4^+/CD8^+$
Observation	38	Before treatment	53.42±10.46	29.32±9.64	1.07±0.24
		After 2 courses of treatment	66.37±10.01[1)3)]	33.02±11.36[1)3)]	1.17±0.13[4)]
Control	37	Before treatment	64.21±12.38	30.02±13.28	1.10±0.33
		After 2 courses of treatment	61.57±11.22[2)]	29.32±9.64[2)]	0.92±0.22[2)]

Note: Compared with the same group before treatment, 1) $P<0.05$, 2) $P<0.01$; compared with the control group at the same time point, 3) $P<0.05$, 4) $P<0.01$

4 Discussion

Cancer pain is the sensation caused by the information that the pain area needs to be repaired or modulated transmitting to the nerve center. Long-term persistent pain makes cancer patients suffer from physical and mental torture, seriously affecting the QOL and mental state of the patients, causing fear, anxiety and depression[6-7]. Multiple studies confirmed that cancer pain had an inhibitory effect on the body's immune system[3-5,8]. The levels of $CD3^+$, $CD4^+$, $CD8^+$ and interleukin-2 (IL-2) in patients with cancer pain were significantly lower than those in cancer patients without pain, and those during pain were significantly lower than those during pain remission[9-10]. Although opioids are the main method for treating cancer pain, long-term use of opioids may have a wide-range inhibitory effect on the body's immune system[11-12], which can cause T lymphocyte apoptosis[13] and inhibit the activation, proliferation and secretion of IL-2 by T lymphocyte[14-17] and tumor necrosis factor-α (TNF-α)[18]. Therefore, long-term use of opioids aggravates the immunosuppression in patients with cancer pain.

The mechanism of cancer pain is very complicated, mainly including the following four aspects: systemic or local inflammatory response; pain caused by tumor directly; pain caused by bone metastasis; neuropathies. The three-step analgesic ladder principle established by the World Health Organization (WHO) is the preferred treatment for cancer pain currently. Acupuncture as a green treatment without obvious adverse reactions has been gradually receiving the attention of the world. The *NCCN Clinical Practice Guidelines in Oncology* has recommended acupuncture, transcutaneous electrical nerve stimulation (TENS) plus medications as one of the comprehensive interventions for cancer pain[19].

In Chinese medicine, cancer pain falls under the category of 'pain syndrome'. Its causative factors include blood stagnation, damp-heat, yin deficiency, qi stagnation, qi deficiency, dampness and retained cold. Its pathogenesis can be divided into two parts: 'the obstruction causes pain' and 'the malnourishment causes the pain'. Acupuncture therapy can regulate meridians to transport nutrition, connect internal with external and move qi and blood by stimulating acupoints, thus achieving analgesia and improvement of immune function. At present, the efficacy of acupuncture analgesia has been widely recognized in

the world and included in the NCCN guideline for pain treatment. Studies have found that acupuncture, moxibustion and acupoint-injection can significantly increase the contents of $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ and IL-2, and the expression of IL-2 mRNA in human body, and improve the lymphocyte immune hypofunction in patients with cancer pain[20-24].

In this study, there was no significant change in the NRS score after treatment in the two groups. The 24 h equivalent morphine consumption in the control group increased significantly after treatment, while remained at a stable level in the observation group. Moreover, after 2 courses of treatment, the 24 h equivalent morphine consumption in the observation group was significantly lower than that in the control group (P<0.05). The above results indicated that although moxibustion with seed-sized moxa cone did not have significant effect on analgesia, it could significantly reduce the consumption of opioid drugs in patients with cancer pain, which could partially explain the certain efficacy of moxibustion with seed-sized moxa cone for patients with cancer pain. In addition, there were no significant differences in $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ levels between the two groups before treatment. However, after 2 courses of treatment, the $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ levels in the control group showed a downward trend, while the observation group showed an upward trend and were significantly higher than those in the control group, which indicated that moxibustion with seed-sized moxa cone could effectively improve the immune function of patients with cancer pain. However, whether it has long-term efficacy in improving immune function of the patients remains to be confirmed.

This study showed that although moxibustion with seed-sized moxa cone did not significantly relieve pain in patients with moderate-to-severe cancer pain, it could effectively reduce the consumption of opioids, and improve the immune function of patients with cancer pain. Moreover, it is easy to perform, economic and safe, and thus is worthy of clinical promotion.

Conflict of Interest

The authors declare that there is no conflict of interest.

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Statement of Informed Consent

Informed consent was obtained from all individual participants.

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Translator: Zhang Fu-qing (张馥晴)