

Clinical Investigation of the Effect of Cancer Pain Plaster in the Treatment of Patients with Moderate to Severe Cancer Pain

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Abstract

Objective: To investigate the effect of applying Cancer Pain Plaster in the treatment of patients with moderate to severe cancer pain.

Methods: A total of 100 patients with moderate to severe cancer pain admitted to our hospital from May 2019 to June 2020 were recruited. The patients were divided into the control group and the treatment group using a random number table method. Thirty patients were divided into the control group and 70 into the treatment group. The patients in control group received three-step cancer pain control therapy. The patients in treatment group received additional Cancer Pain Plaster on basis of the three-step therapy. The effect of pain relief and safety after treatment were compared between the two groups.

Results: The rate of complete pain relief in the treatment group was significantly higher than that of the control group (52.92% vs. 26.08%, $P < 0.05$), and the rate of inefficiency in the treatment group was significantly lower than that of the control group (10% vs. 31.25%, $P < 0.05$). The incidence of adverse effect in the treatment group was lower than that in the control group (2.25% vs. 8.08%, $P < 0.05$).

Conclusion: The application of Cancer Pain Plaster to patients with moderate to severe cancer pain can effectively relieve the pain of the patients and improve their life quality. It is worthy of clinical application.

Keywords: moderate to severe cancer pain; Cancer Pain Plaster; three-step drug pain control therapy.

1. Introduction

Cancer pain is one of the most important symptoms of advanced tumors. Patients with advanced tumors suffer from cancer pain that is difficult to effectively be controlled and will seriously affect the patients' life quality. To effectively control cancer pain, improve the survival time and life quality of tumor patients has become a major concern in the medical studies. In order to ensure the pain of patients can be effectively relieve, analgesic therapy should be taken to extend the comfort period during the survival of tumors

patients.^[1] Although the three-stage cancer pain therapy recommended by the WHO works effectively, adverse reactions such as gastrointestinal symptoms (constipation, nausea, vomiting), neurophysiological symptoms (hypersomnia, disturbance of consciousness), the ceiling effects brought by the long-term use of these drugs are also noticed by the clinicians. Long-term use of opioids reduces the pain threshold and increases the tolerance of the patients, making the effect unstable. Besides, about 30% of tumor patients cannot effectively relieve their pain by the therapy. Under such situation, in-depth research on the treatment of cancer pain with Chinese medicine was promoted.

As patients with advanced cancer pain have qi deficiency, making them vulnerable to aggressive treatment, weakened absorption function of the spleen and stomach, the effect of oral medication alone is not effective. External therapy of Chinese

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medicine, such as acupuncture, acupoint application, and Chinese medicine fumigation could play a role in such cases. Therefore, the application of traditional Chinese medicine for cancer pain has attracted more and more attention, and the external patch of cancer pain plaster with Chinese medicine characteristics has gradually been promoted.

Cancer Pain Plaster is the experience prescription for cancer pain created by Professor Tang Nong from Guangxi University of Traditional Chinese Medicine. It is composed of cooked aconite, sulfur, oyster, frankincense, myrrh, dragon's blood, asarum, etc. It has the effects of warming the cold, removing the stasis, dredging meridian, promoting qi to relieve pain, detoxification and anticancer. Professor Tang summarized the pathogenesis of cancer pain, "Yang deficiency and qi stagnation, accumulation of yin and blocked meridian", combined with the theory of "internal disease and external treatment" in Chinese medicine. Tang's application of Cancer Pain Plaster is used to make the drug work from the outside to the inside directly, softening and dispelling knots. Cancer Pain Plaster promotes blood circulation, relieves pain, alleviates the suffering of patients, improves the life quality of the patients and prolongs their survival time rapidly and effectively, especially for patients with advanced cancer who have difficulty in taking food and incapacity of receiving Western medicine.

Based on the effectiveness and advantages of traditional Chinese medicine in the treatment of cancer pain, in this study, we investigated the effect of Cancer Pain Plaster in the treatment of patients with moderate to severe cancer pain by recruiting 100 patients with moderate to severe cancer pain admitted to our hospital.

2. Materials and Methods

2.1 General data

A total of 100 patients hospitalized in the Affiliated Hospital of Guangxi University of Traditional Chinese Medicine from XX to XX were included. All patients were clinically diagnosed with advanced cancer and according to X-ray, CT, ECT, pathology and cytology, and clinical examination, all the patients were suffering from cancer pain and required medication. There were 68 male patients and 32 female patients. The age of the patients ranged from 39-73 years old, with an average age of 62.5 years. Distribution of disease types: 26 cases of primary liver cancer, 25 cases of lung cancer, 23 cases of gastric cancer, 10 cases of colorectal cancer, 9 cases of breast cancer, 4 cases of multiple

myeloma, and 3 cases of pancreatic cancer. Among them, there were 20 cases of lung metastasis, 8 cases of bone metastasis, and 8 cases of pancreatic metastasis. All of the patients had moderate to severe pain, and 96.6% of patients had a history of receiving analgesics or treatment. In terms of Traditional Chinese Medicine (TCM) syndrome differentiation, patients were divided into qi stagnation and blood stasis type, qi and yin deficiency type, and phlegm-dampness type. It is believed that the pathogenesis lies in "Yang deficiency and qi stagnation, accumulation of yin and collateral failure". All patients took neither analgesic drugs nor other auxiliary drugs within 24 hours before treatment with Cancer Pain Plaster. All patients were randomly divided into two groups: 30 cases in the control group and 70 cases in the treatment group. There were no significant differences in gender, age, symptom, type of disease, and degree of cancer pain between the two groups ($P > 0.05$), and they were comparable.

2.2 Treatment method

2.2.1 Control group

Patients in the control group were treated with three-step medication for pain relief. Codeine (Qinghai Pharmaceutical Factory Co., Ltd., National Medicine Standard H10980104) was given to patients with moderate pain, 30mg each time, 12 hours apart, for 2 days. Tramadol capsules (manufactured by Germany Grantai Co., Ltd., batch number: 921A) were given to severe patients, 20mg each time, 12 hours apart, for 2 days.

2.2.2 Treatment group

For patients in the treatment group, the Cancer Pain Plaster treatment was added to the treatment of the above-mentioned control group patients. The painful part of the patient was cleaned first. The acupoints used in this experiment were as follows: Feishu acupoint on both sides for lung cancer; Guanyuan acupoint for gastric cancer and liver cancer; Tanzhong and Jimen acupoints for breast cancer; Muhe acupoint for colorectal cancer; Shenque, Zusanli, Yongquan, and Ashi acupoints for pancreatic cancer; Yongquan and Sanyinjiao acupoints for multiple myeloma. We took 2-3 sticks each time, 24 hours replacement, 3 days as a course of treatment.

Cancer Pain Plaster is composed of cooked aconite, sulfur, oyster, frankincense, myrrh, dragon's blood, asarum, etc. After extracting and purifying the effective ingredients of the drug, combining the matrix molding process and the

preparation molding process, the product is tested by HPLC. To carry out inspections, we used TLC method to identify the samples, established HPLC method to determine content, and conducted system suitability test, negative control test, linearization range test, stability test, precision test, repeatability test, sample recovery rate test, sample content determination, etc., and determined the content limit range of the sample. All patients treated with the plaster have not received radiotherapy, chemotherapy and other treatment therapy recently. All patients have no intellectual disability. They can clearly judge their pain levels, and have normal language organization and expression skills. Then we evaluated the life quality and pain relief of the patients.

2.3 Observation indicators

The effect of pain relief and safety were evaluated according to the standard therapy of "Cancer Pain Diagnosis and Treatment Specification". The degree of pain and the degree of pain relief were graded by the Verbal Rating Scale (VRS) and Visual Analogue Scale (VAS).

The VRS method divides pain into four levels as following: Grade 0, painless; Grade 1, bearable pain, able to live a normal life without affecting appetite and sleep; Grade 2, obvious pain, affecting appetite and sleep and in need of analgesics; Grade 3, obvious and unbearable pain, severely affecting sleep and appetite and in need of analgesics

The VAS method also divides pain into four types. No Relief (NP): no obvious effect after and before treatment, no pain relief, and sleep is severely affected; pain reduction is less than 2 points; Mild Relief (MR): pain is reduced by 3-4 points compared to before administration, obvious

pain can be felt, and sleep will be affected; Partial Relief (PR): pain is reduced by 5-7 points compared to before administration, sleep is basically not affected, and the patient can live normally; Complete Relief (CR): pain is reduced by 8 points or more compared to before the administration, and patients are completely painless.

The life quality is divided into four levels according to the Karnofsky scoring standard. Significant improvement: score increases by 20 points or more; Improvement: score increases by 10-20 points; Stable: no significant change in score (5-10 points); Decrease: score decreases by 5 points and more.

2.4 Statistical method

The Excel 2013 was used to establish a database, for entering and sorting the data. The SPSS 21.0 statistical software was used for data processing. The comparison between groups was performed by Chi-square test and t test. $P < 0.05$ indicated significant difference, with statistical significance. $P < 0.01$ indicated extremely significant difference, with statistical significance.

3. Results

The pain degree, part, duration and life quality were recorded. Attention was paid to the adverse reactions of the patients during the experiment. Chi-square test was used to compare the differences in gender and staging between the two groups. t-test was used to compare the differences in patient age. As for the patient gender, $\chi^2 = 0.2817$, $P > 0.05$, without significant difference. As for the patient staging, $\chi^2 = 0.067$, $P > 0.05$, without significant difference. As for the patient age, $T = 0.06$, $P > 0.05$, without significant difference. (Table 1)

Table 1. General analysis of cases in the treatment group and control group

Group	Gender		Age		Staging		Diseases					
	M	F	39-65	52	18	21	17	19	4	4	0	5
Treatment Group	45	25	39-65	52	18	21	17	19	4	4	0	5
Control Group	23	7	43-73	22	8	4	6	7	6	0	3	4

3.2 Analysis of curative effect

3.2.1 Comparison of pain relief effect between the control group and the treatment group

The rate of complete pain relief in the treatment group was significantly higher than that of the control group (52.92% vs. 26.08%), and the rate of

inefficiency in the treatment group was significantly lower than that of the control group (10% vs.

31.25%). The differences in data comparison have statistical significance ($\chi^2=7.94$, $P<0.05$) (Table 2).

Table 2. Curative effect of Cancer Pain Plaster on cancer pain 【n=%】

Group	Case No.	CR	PR	MR	NR
Treatment Group	70	37 (52.92%)	13	13	7 (10%)
Control Group	30	8 (26.08%)	8	5	9 (31.25%)

3.2.3 By rank sum test, $u_c = 2.404$, $P < 0.05$, the difference between the two groups is significant!

In the experimental process, only one female case in the treatment group of 70 patients showed local itching and congestion of the skin after using Cancer Pain Plaster, and the symptoms disappeared after the injection of 25mg of promethazine. No

adverse reactions occurred after continuous use. No side effects such as addiction, nausea and vomiting, dizziness and drowsiness were observed. However, Tramadol capsules taken by the control group had many side effects, including dizziness (two cases), panic attacks (one case) and nausea (one case). (Table 3)

Table 3. Changes in life quality of patients with cancer pain treated by Cancer Pain Plaster

Group	Case No.	Significantly improved (≥ 20)	Improved (10-20)	Stable (-5-10)	Decrease (≤ -5)
Treatment Group	70	15	37	18	0
Control Group	30	9	15	5	1

3.3 Analysis of curative effect for different pain levels

Through treatment to the treatment group and the control group, the daily pain levels of the patients were recorded by combining both VRS and VAS methods. Additionally, the patients were asked to use the Karnofsky scoring standard to evaluate their life quality after the treatment based on their appetites, spirits, sleep status, etc.

According to Table 2, it can be seen that in terms of treatment effect, the Cancer Pain Plaster does play a vital role in helping cancer patients relieve or even eliminate the cancer pain. On the other hand, Cancer Pain Plaster has no obvious side effects, whereas Tramadol Capsule leads to adverse reactions such as nausea, vomiting, etc. on patients which affect their life quality, though it has evident effects in treating cancer pain. With respect to life quality, there was a significant difference between the treatment group and the control group according to the results of data processing. The Cancer Pain Plaster treatment had improved the quality of patient's life significantly.

3.4 Analysis of curative effect for different TCM (Traditional Chinese Medicine) Symptoms

As introduced in the general information, it is proposed that in TCM syndrome differentiation, patients were divided into three types according to their reactions after receiving treatment. It showed that after 30 minutes of medication, along with local fever, there was analgesic effect as well. Among all the disease types, the total effective rate of Cancer

Pain Plaster reached 85.7%. According to detailed data, it is found that a certain relationship exists between TCM syndrome and the specific curative effect. The highest effective rate of the Cancer Pain Plaster was for qi stagnation and blood stasis type of cancer pain, which was up to 91.2%, followed by 82.3% effective rate for phlegm-dampness type of cancer pain and a lowest effective rate of 63.9% for qi and yin deficiency type of cancer pain. The current analysis is only based on TCM syndrome differentiation, and the specific relationship needs to be further explored based on expertise in TCM and Science of Chinese Pharmacology.

4. Discussion

Pain is a major and common complication for cancer patients. Pain is not only caused by harmful stimuli to the body. Patient's mental state, psychological state and socio-economic factors can also aggravate the degree of pain, resulting in reduction of their life quality. According to the statistics of the WHO (World Health Organization), there are more than 500,000 cancer patients in the world suffering from daily pain. The cancer pain seriously threatens the patient's life quality; hence pain relief has become one of the important research contents to improve cancer patients' life quality.

Although "three-step medication for pain relief" controls many patients' pain to some extent, it has toxic side effects as well. It is easy to develop tolerance and difficult to maintain for a long time. Besides, the long-term use of opioid drugs

generates poor effect, and is easy to present adverse reactions^[3] such as constipation, nausea, movement and cognitive impairment, respiratory depression, dependence on drugs, etc.

This situation has prompted in-depth research on the treatment of cancer pain by TCM. As patients with advanced cancer pain have qi deficiency, making them vulnerable to aggressive treatment, weakened absorption function of the spleen and stomach, the effect of oral administration alone is not effective. External treatment of Chinese medicine shows its advantages. Its outstanding advantages are: safety in use, light toxic and side effects and almost no drug dependence; it can not only relieve pain, but also has the effect of anti-tumor and cancer, treating both symptoms and causes.

The external treatment makes the drug first form a higher concentration in the skin, pores, acupoints and other tissues by applying medicine to the outside, so that the toxin will be dispelled or dispersed, and the local qi and blood will be dredged to ease the pain; at the same time, the drug reaches the focal zone through absorption by skin and mucosa and the transmission of meridian, in order to achieve overall treatment effect such as meridian dredging, detoxification, stasis removal, and reconciliation of qi.

With respect to the mechanism of pain, there are TCM theories such as "pain is caused when there is stasis" and "toxin amassment causes more pain". With respect to the treatment of pain, there are theories such as "all pains are caused by excess and pains are reduced with excess-removal" and "no stasis makes no pain", especially emphasizing that excess-removal therapy is essential to relieve pain. The pathogenesis of cancer pain lies in overall "deficiency" and local "excess", which can be boiled down to "stagnation and deficiency". Based on the TCM theory of "internal disease with external treatment" and the characteristics of local pathogenesis, the Cancer Pain Plaster is adopted as an external treatment following the basic principle of "invigorating blood to eliminate stasis, warming and promoting circulation of qi". Powerful drugs like Musk, Radix Aconiti Kusnezoffii, Toad Venom, etc. are used to warm the cold, relieve pain and regulate qi and blood circulation.

The key pathogenesis for cancer pain lies in the imbalance of qi and blood circulation, so Rhizoma Corydalis and Clove are used to regulate qi, and Salvia Divinorum, Frankincense, Myrrh, Common Burreed Rhizome, Curcumae Rhizoma, etc. are used to invigorate blood, to promote smooth circulation

of local qi and blood and relieve pain. Borneol and Salvia Divinorum are used to tranquilize the mind and nourish the heart, etc., which helps protecting central nervous system and reducing adverse reactions of the system to malignant stimulation of cancer pain.

A malignant tumor is what the TCM calls "malignant sore". It is formed due to the deficiency of qi and dysfunction of viscera that lead to qi stagnation, blood stasis, phlegm condensation and toxic accumulation. Using a plaster formula collected from Anhui folk and improved for external treatment of cancer has the efficacy of resolving cancer toxins, removing phlegm, scattering knots, promoting blood circulation and relieving pain. This plaster is powerful and is limited to external use only without harm to qi. With musk serving as the principle drug, the plaster promotes blood circulation, removes stasis and relieves pain. According to the *Compendium of Materia Medica*, musk "can remove excess at various orifices and open up the stagnation of meridians", and it is a cure for "internal block".

As the minister drug, Arsenolite can remove canker and fight poison with poison. In recent years, researches show that, Pinellia Ternata and Arisaema with Bile can disperse knots, Salvia Miltiorrhiza and Rumo Powder can nourish and activate blood, and Common Monkshood Mother Root and Nux Vomica can dredge collaterals, scatter knots, reduce swelling and relieve pain. The combined use of these drugs contributes to resolving cancer and detoxifying, removing phlegm and scattering knots, promoting blood circulation and relieving pain. The overall intention is not only to relieve pain, but also to resolve cancer and remove tumor targeted at the pathogenesis of cancer, so as to deal with both symptoms and root causes.

As the drug is a pure Chinese medicine preparation, long-term use will not lead to addiction. Local application on the skin and continuous absorption through the skin greatly extends the duration of pain relief with no gastrointestinal stimulation occurred. The Cancer Pain Plaster can be used as a secondary drug, and it can also reduce the dosage of tertiary drug, thus reducing the risk of opioid overdose.

Although TCM has advantages in cancer pain treatment such as light side effects, low resistance and addiction to drugs, accurate curative effect and improvement of other related symptoms, it also has many shortcomings: (1) the active ingredients of some anti-cancer and analgesic TCM are unknown, and the drug research and action mechanism are

unclear. (2) The dosage forms are relatively single, mostly traditional Chinese herbal preparations such as pill, powder, paste, medicine ball, etc. Most of the preparations need to be boiled in pots and pottery jars, which could mess up the clothes during use and incapacitates activities. Moreover, the quantification is not precise and normalized, resulting in large deviation in treatment effect, thus affecting the evaluation of its efficacy.

Therefore, it is necessary to pay attention to and strengthen the research on the active ingredients of TCM, improve the curative effect of TCM, develop components for new drugs, and provide a basis for the quality control of TCM preparations, which are also necessary conditions for international recognition^[11]. In addition, accelerating the reform of dosage form and improving the preparation level are key measures to improve curative effect. Research on the curative effect standards of TCM in malignant tumor treatment should be strengthened. The new curative effect standards shall not only notice the changes of local lesions, and reflect the importance of clinical benefit indicators such as pain, life quality, diet, sleep, and physical fitness, but also include the observation of curative effect with median survival time as a long-term indicator^[12].

5. Conclusion

Since most tumor patients suffer from severe pain in advanced stages, failure to get effective relief can jeopardize their survival treatment^[4]. Currently, WHO recommends the use of three-step drug pain control therapy, but the effect is limited.

In order to further relief, the pain of patients with moderate to severe cancer pain, research on other effective treatment methods must be strengthened. According to the Chinese medical science research on the effect of applying Cancer Pain Plaster in the treatment of patients with moderate to severe cancer pain, the results showed that the rate of complete pain relief in the treatment group was significantly higher than that of the control group (52.92% vs. 26.08%), and the rate of inefficiency in the treatment group was significantly lower than that of the control group (10% vs. 31.25%). The differences in data comparison have statistical significance ($P < 0.05$). It indicates that the external application of Cancer Pain Plaster can significantly reduce the pain level of patients, improve their quality of life, extend their comfort period, and boost their confidence in treatment. So, the patients will actively cooperate with the treatment and improve treatment effect.

The incidence of adverse effect in the treatment

group was lower than that in the control group (2.25% vs. 8.08%, $P < 0.05$). The differences in data comparison have statistical significance. It indicates that the external application of Cancer Pain Plaster is safe and also helpful in reducing the adverse effects brought about by the three-step drug pain control therapy. The external application of TCM has a long history, and according to the *Rhymed Discourse for Topical Remedies*, "the essence of external treatment is the internal treatment". According to the *The Origin and Development of Medicine*, "the medicine penetrates the skin into tissues which stimulates the circulation of collateral channels. It is particularly effective compared with oral administration. It is a wonderful method."

The external treatment of TCM is easy to be applied, with little toxic side effects and fast efficacy. Moreover, it is able to avoid the deactivation of digestive tract and digestive enzymes in the liver. It is an important route of administration that cannot be ignored, especially suitable for patients with moderate to severe cancer pain. The Cancer Pain Plaster has good analgesic effect on cancer pain. Experimental results have also shown that the external treatment of TCM has great application value and no obvious side effects for clinical severe tumor. Therefore, it is worthy of further clinical application.

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