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Research Progress of Traditional Chinese Medicine External Treatment for Cancer Pain

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Abstract: Cancer pain, as a common complication in patients with malignant tumors, is regarded as the fifth vital sign. The involvement of traditional Chinese medicine (TCM) in the treatment of malignant tumors has become a distinctive feature of oncology treatment in China. It is also an important component of cancer pain management. TCM analgesic treatments include various methods, such as internal medicine and external therapies. External analgesic therapies, in particular, are significant methods in TCM pain management and offer both local treatment and systemic regulation. These methods are simple, easy to perform, and non-invasive. They can enhance pain relief effects while reducing the difficulty of oral medication intake and avoiding adverse gastrointestinal reactions, providing new perspectives and approaches for cancer pain treatment with broad development prospects. This article provides a review of the external TCM therapies for cancer pain to share with peers in the field.

Keywords: Cancer pain; External treatment of traditional Chinese medicine; Research progress

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1. Introduction

Cancer pain primarily refers to pain caused by the direct invasion of surrounding tumor tissues or distant metastasis, as well as induced by anti-tumor treatments, such as surgery and radiotherapy. As one of the common complications in patients with malignant tumors, the main characteristics of cancer pain include persistent pain, often accompanied by sudden pain. The nature of the pain mainly includes pain that resembles burning, stabbing, tearing, and cutting. Data surveys show that the incidence of pain in newly diagnosed malignant tumor patients is about 25%. In comparison, the incidence in patients with advanced malignant tumors can reach 60% to 80%, with about one-third of the patients experiencing severe pain [1]. Currently, the treatment for cancer pain mainly follows the "three-step analgesia" treatment principle advocated by the World Health Organization (WHO), while some of them still bear unsatisfactory analgesic effects [2,3]. Moreover, the adverse reactions caused by opioid drugs, including constipation, nausea, and vomiting, impose a heavy burden

on cancer patients. Traditional Chinese Medicine (TCM) external therapy, as an adjunct analgesic method, is characterized by convenience, significant efficacy, and economic safety. This article summarizes the treatment of cancer pain with TCM external therapy, hoping to provide thoughts and methods for the clinical TCM treatment of cancer pain.

2. Dialectical thinking

Cancer pain is classified under the "pain" category based on its clinical manifestations in TCM. The main etiologies and pathogenesis include "pain due to obstruction" and "pain due to lack of nourishment." Excess syndromes are often seen with conditions such as cold congealing, Qi stagnation, and blood stasis. In contrast, deficiency syndromes are often associated with depletion of fluids, Yang deficiency, and organ deficiency. The pathogenic factors are often intertwined, with both excess and deficiency coexisting, making the pathogenesis increasingly complex [4]. Professor Li Peiwen has a unique approach to the differentiation of cancer pain, comprehensively using methods such as warming Yang to disperse cold, activating blood to unblock the collaterals, promoting Qi to dissolve stagnation, resolving phlegm to regulate Qi, clearing heat to detoxify, and softening hardness to disperse knots. Based on these methods, he incorporates "site-specific" TCM herbs, such as Qianhu, Gualou, and *Houttuynia cordata* for lung cancer pain, and rose, August melon, and lychee core for breast cancer pain, the combination of herbs and treatment methods effectively alleviates cancer pain [5].

Professor Li Suling categorizes primary liver cancer pain into four types: excess pain, deficiency pain, cold pain, and heat pain [6]. Accordingly, he classifies liver cancer pain into seven syndromes: Qi and blood deficiency, liver Qi stagnation, phlegm-damp stagnation, Yin deficiency with fluid depletion, Qi stagnation and blood stasis, Yang deficiency with cold congealing, and heat toxin accumulation. He innovatively proposes the "One tonification and four attacks" method for treatment, in which "tonification" aims to support the body's proper energy, and the "attack" involves clearing heat toxins, eliminating blood stasis, promoting bile discharge, and using toxins to attack toxins. He first emphasizes distinguishing between "deficiency in the right and excess in the evil," then differentiating between cold and heat, achieving significant results.

Professor Hua Baojin believes that cancer pain often arises from "pain due to obstruction," where the Yang Qi in malignant tumor patients becomes obstructed, leading to the formation of metabolic products such as Qi stagnation, water retention, and phlegm-dampness, which hinder the circulation of Yang Qi and cause pain [7]. Based on the etiology and pathogenesis, he proposes the method of unblocking yang to treat cancer pain, emphasizing "unblocking Yang" rather than "warming Yang." He selects penetrating herbs to enable Yang Qi to circulate throughout the body, which can be divided into methods such as unblocking yang to dissolve nodules and unblocking Yang to promote water metabolism and resolve dampness. By enabling the circulation of Yang Qi, it is expected to warm and nourish the entire body, thereby alleviating cancer pain and other symptoms. In summary, although different TCM practitioners have various understandings of the etiology and pathogenesis of cancer pain, they all focus on the dual aspects of "excess and deficiency." Based on syndrome differentiation, combined with the characteristics of the pathogenesis, they choose specific treatment methods such as activating blood, benefiting Qi, resolving phlegm, and dissolving nodules, achieving good therapeutic effects.

3. External treatment of TCM

TCM external therapy has a long history and the "Li Yue Pian Wen" records that: "The principles of external treatment are the same as those of internal treatment; the medicines used for external treatment are the same as those for internal treatment, differing only for their method." Modern researchers believe that advanced tumor

patients often have undergone treatments such as radiotherapy, chemotherapy, and targeted therapy, leading to deficiency in their body's vital energy and weakness in the spleen and stomach. Oral medications at this period can burden the spleen and stomach, causing poor appetite and impaired digestion. External therapy can alleviate pain through skin, meridians, and acupoints [8]. Current TCM external therapies for cancer pain treatment include acupuncture, moxibustion, and external application of medicinal plasters. The following content is a brief overview of the progress of these treatments.

3.1. Acupuncture

Acupuncture, as one of the effective TCM external therapies for cancer pain, is known for its convenience and high safety. Li D *et al.* (2020) conducted a study on 60 patients with moderate to severe cancer pain [9]. The control group was treated with oral oxycodone hydrochloride sustained-release tablets, while the observation group combined this treatment with acupuncture. The results showed that the cancer pain relief rate in the observation group was 90.0%, significantly higher than that of 76.7% in the control group. Moreover, the combination of acupuncture reduced the dosage of analgesic drugs. He Y *et al.* (2021) reviewed databases and included clinical research data from 28 studies on acupuncture for cancer pain [10]. They designed a Delphi survey questionnaire to analyze and summarize the acupuncture point selection patterns and high-frequency acupoints for cancer pain treatment. The results indicated that acupuncture point selection for cancer pain should follow a personalized approach, with primary points including Zusanli (ST36), Taichong (LR3), Hegu (LI4), Yanglingquan (GB34), Sanyinjiao (SP6), and Ashi points, providing evidence basis for clinical acupuncture treatment of cancer pain. In recent years, there also have been advancements in the research on the mechanisms of acupuncture for cancer pain relief [11]. Studies showed that acupuncture could transmit impulses to the spinal cord, activate higher central releases of descending inhibitory impulses to achieve analgesia, and integrate pain signals in the cerebral cortex and spinal cord to exert a collective analgesic effect. Additionally, the analgesic mechanism of acupuncture is related to the synthesis and release of large amounts of serotonin (5-HT) in the brain [12]. Thus, acupuncture can determine different treatment principles and methods through syndrome differentiation and point selection, adhering to individualized principles, and achieving good results in cancer pain management.

3.2. Moxibustion

Moxibustion for pain relief involves the use of moxa to heat specific acupuncture points, combining external moxibustion with acupoints to achieve analgesic effects. Chen J *et al.* (2020) conducted a randomized study on 120 cancer pain patients where both groups received oral oxycodone hydrochloride sustained-release tablets as the basic analgesic treatment [13]. The treatment group additionally received moxibustion on the back-shu points, specifically bilateral Jueyinshu (BL14), Ganshu (BL18), Danshu (BL19), Shenshu (BL23) and Sanjiaoshu (BL22), each point for 5 minutes, ensuring that patients felt warm sensation without burning pain. They compared the NRS scores and pain improvement rates before/after treatment and measured the levels of IL-6 and TNF-α in peripheral blood. The results showed that the treatment group had better pain assessment and improvement rates than the control group ($P < 0.05$), and significantly inhibited the expression of IL-6 and TNF-α ($P < 0.05$). The preliminary evidence suggests that moxibustion on back-shu points can be analgesic by inhibiting the expression of inflammatory factors IL-6 and TNF-α. Ouyang J *et al.* (2018) randomly divided 120 cancer pain patients into a treatment group (60 patients) and a control group (60 patients) [14]. Both groups received conventional three-step analgesia treatment, while the treatment group additionally received warming yang moxibustion. The basic acupoints were Zhongwan (RN12), Shenque (RN8) and Guanyuan (RN4), with

additional points for specific pain locations: Yangbai (GB14), Hegu (LI4) and Zusanli (ST36) for forehead pain; Taiyang (EX-HN5), Shuaigu (GB8), Yanglingquan (GB34) and Waiguan (SJ5) for lateral head pain. After 4 weeks, the NRS scores of the treatment group decreased significantly compared with the control group ($P < 0.05$). Furthermore, compared with using the three-step analgesia treatment alone, the treatment group showed significant improvement in quality of life (including sleep, mental state, and daily activities) after using warming yang moxibustion ($P < 0.05$), further confirming the effectiveness of moxibustion for cancer pain. Moxibustion can promote blood circulation and unblock meridians through its warming effect, relieving cancer patients' pain. However, moxibustion mainly targets cold syndrome cancer pain patients. Further exploration is needed to verify its analgesic effects on other types of cancer pain.

3.3. External application

The external application of medicinal plasters involves using herbal ointments or patches applied to the pain area for transdermal absorption to achieve analgesic effects. Li H *et al.* (2021) divided 60 cancer pain patients into a study group and a control group, each with 30 patients [15]. The control group received treatments such as ibuprofen sustained-release capsules, tramadol hydrochloride sustained-release tablets, and oxycodone hydrochloride sustained-release tablets based on the severity of the pain. The study group received these treatments in combination with the external application of compound soapwort thorn ointment to evaluate its efficacy and safety in cancer pain. The results showed that the combination of oral analgesics with the external application of the compound soapwort thorn ointment significantly reduced the patients' NRS scores ($P < 0.05$), decreased medication dosage, and improved quality of life. Liang Y *et al*. (2021) believed that the occurrence of cancer pain is often due to "toxins and stasis" blocking the meridians [16]. They used the Shuanghuang Sanjie Powder, which performed heat-clearing, detoxifying, and pain-relieving properties, for external application in combination with opioid medications. The results indicated that the combined use of Shuanghuang Sanjie Powder with opioids significantly improved patients' quality of life, shortened the time to pain relief, reduced the frequency of breakthrough pain, decreased the dosage of opioids, and reduced adverse reactions compared to using opioids alone ($P < 0.05$). Yu Y (2020) randomly divided 60 liver cancer patients with mild to moderate cancer pain of Qi stagnation and blood stasis type into the treatment group and control group, each with 30 patients [17]. The control group received acetaminophen and dihydrocodeine tablets for pain relief, while the treatment group combined these with the external application of Aitong Powder. The results showed that the treatment group had significant improvement in pain relief, reduced pain duration, and improved TCM clinical symptoms compared to the control group ($P < 0.05$), confirming the effectiveness of Aitong Powder for patients with mild to moderate liver cancer pain of Qi stagnation and blood stasis type. In conclusion, the external application of medicinal plasters for cancer pain is relatively simple, easy to manage, does not interfere with the patient's daily activities, and can be used as an adjunct to standard analgesic treatments.

3.4. Acupoint injection

Acupoint injection involves using specific drugs injected into the body's designated acupoints to achieve analgesic effects. Guo H (2019) randomly divided 100 advanced cancer pain patients into two groups, the control group received oral morphine sustained-release tablets for pain relief, while the observation group received acupoint injections in addition [18]. The specific method involved disinfecting bilateral Ququan (LR8), Xinshu (BL15), and Ganshu (BL18) points and then injecting 2 milliliters of compound Danshen injection every other day. After 4 weeks, the efficacy assessment showed that the total effective rate in the observation group was 88%, significantly higher than the control group's 70% ($P < 0.05$). Additionally, researchers have

explored the analgesic effects of auricular acupuncture. Bai T *et al.* (2019) conducted a study on 97 cancer pain patients and randomly divided them into groups [19]. The observation group received auricular acupoint injections in addition to oxycodone for pain relief and selected primary points corresponding to the disease and auxiliary points such as Jiaogan, Shenmen, and Sanjiao. The injection used was 0.2 to 0.4 mL of compound Danshen injection. After 12 days, the observation group's BPI pain scores were significantly lower than those of the control group ($P < 0.05$) and their depression and anxiety scores also improved significantly ($P < 0.05$). As to the choice of injection drugs, different explorations have been made. Luo J *et al.* (2018) randomly divided patients with severe cancer pain into groups [20]. The treatment group received morphine injections at the Zusanli (ST36) with a dose of 5 mg. After one month, compared to patients receiving intramuscular injections, those who received morphine injections at Zusanli (ST36) had significantly faster onset times, longer maintenance of analgesic effects, and fewer adverse reactions ($P < 0.05$). Additionally, this method improved the expression of $CD3^+$, $CD4^+$, and the $CD4^+/CD8^+$ ratio, while reducing NK cell expression, thus enhancing immune function. In summary, acupoint injection can be of analgesia for cancer pain patients. However, current research on the analgesic effects of acupoint injection mainly consists of small-scale clinical observations. There is no consensus on the drugs used and acupoints selected, often based on personal experience. Issues such as off-label drug use and inconsistent injection dosages require further exploration.

4. Discussion

Cancer pain, as one of the common complications in patients with malignant tumors, severely affects patients' quality of life and can even hinder the normal course of treatment [21]. Current researches on the mechanisms of cancer pain suggest that it results from multiple factors, including the influence of the tumor microenvironment [22], microglial activation [23], central and peripheral nerve sensitization [24,25], and the activation of multiple signaling pathways [26-28]. The treatment largely follows the "three-step ladder" approach proposed by the World Health Organization, which involves assessing the pain level based on the patient's specific conditions, such as complaints, medical history, symptoms, and signs. As the pain is categorized into three levels: mild, moderate, and severe, with medication administered accordingly. The treatment model is widely used for its effectiveness and convenience [29]. However, there are still gaps in the understanding and use of analgesics by some healthcare professionals [30,31]. Additionally, varying regulations on these medications across different regions can lead to inadequate pain control in some cancer patients [32]. Moreover, the main adverse reactions of opioids, such as constipation and nausea, increase the psychological burden on patients. As one of the main methods of TCM for treating cancer pain, TCM external therapy follows the principle of syndrome differentiation and treatment, addressing "pain due to obstruction" and "pain due to lack of nourishment" by using methods such as activating blood circulation, removing blood stasis, tonifying Qi, nourishing blood, clearing heat and detoxifying. Techniques include acupuncture, moxibustion, external application of medicinal plasters, and acupoint injection. These methods help reduce the burden of oral analgesics and provide synergistic pain relief. However, current studies on TCM external therapy for cancer pain mainly involve small sample clinical observations, with subjective patient experiences or scale scores as primary indicators. Point selection and medication often rely on individual practitioners' experience and lack unified standards and in-depth research on analgesic mechanisms. Therefore, further exploration and research are needed to enhance the application of TCM external therapy in cancer pain management, leveraging TCM's holistic approach and the advantages of local treatments to alleviate patients' pain and improve their quality of life.

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