Skin-patch Of Ding Zi Gao on Relieving Local and Systemic Symptoms in Patients with Moderate to Severe Periodic Mastalgia: A Randomized, Double-Blind Trial

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Research

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Abstract

Background and purpose: The use of hormone receptor agent drugs such as androgens (tamoxifen) for the treatment of moderate and severe breast pain has limitations such as cardiac, hepatic, and nephrotoxicity and gastrointestinal side effects. Therefore, there is a need to prescribe a new safe and effective topical treatment method to reduce the use of anti-inflammatory and hormonal agent drugs, the incidence of adverse effects and the financial burden on patients. This randomized controlled clinical trial investigates the clinical efficiency and safety of Skin-patch of **Ding Zi Gao (DZG)** acupoint-application therapy for the treatment of **moderate to severe Periodic mastalgia (MSPM)**, and provides a basis for the design of an optimized, safe and effective comprehensive treatment plan for MSPM.

Methods: Sixty patients with **moderate to severe Periodic mastalgia (MSPM)** who met the inclusion criteria were selected from the breast clinic of Beijing Hospital of Traditional Chinese Medicine affiliated to Capital Medical University and randomly divided into 30 cases in the treatment group and 30 cases in the control group.

The treatment group was treated by Skin-patch of **Ding Zi Gao (DZG)** acupoint-application therapy, which was applied from the 3rd day after the end of menstruation, once a day, for 6-8 h each time, 14 times as a course of treatment, and the treatment was completed within 1 month, and the application was stopped during menstruation. The control group was treated with skin patches of **placebo acupoint application**, and the duration and course of treatment were the same as that of the treatment group. During the 14 day course of treatment and 2-month follow-up after the experiment, the main outcome indicators (including Breast pain improvement onset time, change in breast pain VAS score, change in patient's mood, sleep, Fullness in both flank, (McGill Pain Questionnaire) **MPQ** and secondary outcome indicators (Including changes in breast nodule size and gland thickness guided by breast ultrasound, VAS pain score in the 2-month follow-up at the end of treatment, and adverse reactions), At the same time, the safety of the scheme was evaluated.

RESULTS: There were no differences between the two groups in terms of age, body mass index, history of breastfeeding, family history of breast disease, history of allergies, history of breast surgery, or duration of breast pain (months) before recruitment.

The comparison between pre-treatment and post-treatment showed that the time to onset of breast pain improvement, visual analogue score (VAS) of breast pain, improvement in mood, sleep, fullness in both flank and the **MPQ** were significantly lower in both groups after treatment, and the improvement was more significant in the treatment group than in the placebo control group ($P < 0.05$). Both groups showed significant reductions in improving patient mammography outcomes and VAS pain scores at two months of follow-up, but there were no significant differences between the groups. In terms of safety evaluation, no significant differences in the incidence of adverse events were found.

CONCLUSION: point-application treatment with skin patches of **Ding Zi Gao (DZG)** therapy in patients with **MSPM** improved breast pain and swelling, reduced breast gland thickness, and decreased breast

visual analogue pain score (VAS) and MPQ score. Its efficacy was significantly better than skin patches of **placebo acupoint application** therapy alone. This study provides a basis for the clinical application of DZG for **MSPM**.

Background

Mammary hyperplasia is a common disease in young and middle-aged women, accounting for more than 70% of all breast diseases and seriously affecting the normal life of patients [1, 2]. It is characterized by proliferative pathological changes in the epithelial cells and fibrous connective tissue lining the alveoli and ducts of the mammary glands. The clinical manifestations of breast hyperplasia are breast pain, local thickening of breast tissue or multiple nodules of different sizes [3, 4]. Studies have shown that the occurrence of **breast hyperplasia** may be related to the increased risk of breast cancer. The incidence of breast cancer is significantly higher in patients with severe breast hyperplasia, atypical breast hyperplasia and cystic breast hyperplasia [5]. However, the exact pathogenesis of **breast hyperplasia** is not fully understood. Researchers generally agree that the development of **breast hyperplasia** is closely related to the disruption of systemic hormones and hormone receptors [6, 7]. Currently, The main treatment for the disease is pharmacological or surgical therapy.

However, because these lesions are generally diffusely distributed, surgical excision cannot remove all of the hyperplastic lesions. Therefore, surgery alone is not likely to completely cure this disease. Traditional Chinese medicine external therapy herbal medicine application for the treatment of breast hyperplasia has unique advantages. Its acupoint application takes effect locally, does not pass through the enterohepatic circulation, and has low side effects, which can directly reach the focal location. Therefore, it is very important for us to develop new external therapy drugs to treat breast hyperplasia.

Clinically, the external application of Chinese medicine is an essential treatment modality with a long history and clear efficacy, which is documented in the classics of Chinese medicine. It is recommended for patients who are uncomfortable with oral administration and has the benefit of a lower dose absorbed transdermally. recent reports suggest that the effect mechanism of topical application of herbs may be related to improvement of local microcirculation and promotion of inflammatory absorption[8] .

Skin-patch of **Ding Zi Gao (DZG)** consists of Ding Tong Gao (J drug, pharmaceutical word Z20053390) and Zi Se Xiao Zhong Gao (J drug, pharmaceutical word Z20053389), **an hospital preparation of Beijing Chinese Medicine Hospital Affiliated to Capital Medical University**. ding tong Paste is mainly composed of Chinese herbs such as Angelicae Sinensis Radix (dang gui), carthami Flos (Hong hua), olibanun (ru xiang) and myrrha (mo yao), and previous studies have shown that it has the effect of activating blood circulation, resolving blood stasis and reducing swelling, which can have an analgesic and anti-inflammatory effect.

Clinical studies have proved that **Ding Zi Gao (DZG)** is a very suitable external treatment drug for the treatment of **moderate to severe Periodic mastalgia (MSPM)**, and the degree of breast hyperplasia is significantly reduced after treatment with **DZG**, and the emotional state has been significantly improved.

Consequently, a controlled, randomised and follow-up study protocol was used in this study, employing the ideal methodology to evaluate the efficiency and safety of topical DZG in treating **moderate to severe Periodic mastalgia (MSPM)**.

Materials And Methods

Research design

This trial was designed as a double-blind, randomised, controlled and parallel-group study focusing on the efficacy and safety of **DZG** for the treatment of **moderate to severe Periodic mastalgia (MSPM)**. completed from December 2018 to June 2019 at the **Beijing Chinese Medicine Hospital Affiliated to Capital Medical University**, which is the first tertiary Chinese medicine hospital in Beijing, China, with a wide range of patients. The study was approved by the Ethics Committee of **Beijing Chinese Medicine Hospital Affiliated to Capital Medical University** [Certificate No. 2017BL-034-03] and registered with the Chinese Clinical Trials Registry. All patients provided written informed consent before enrollment.

Diagnostic criteria

Diagnostic criteria of MSPM

For the diagnosis of **moderate to severe Periodic mastalgia (MSPM)**, we can refer to the "Reference Standards for the Diagnosis of Breast Hyperplasia" adopted by the Eighth Meeting of the Chinese Society of Traditional Chinese Medicine and Surgery (CSCM) Specialized Committee on Breast Diseases in 2002

(1) Clinical performance:

Breast tenderness: characterised by pain associated with the menstrual cycle. The pain usually appears or worsens before menstruation (about 7 days before the onset of menstruation) and decreases significantly or disappears completely after the onset of menstruation, but the course of the disease is long and there is no clear regular pattern for the patient to follow.

Breast masses: diffuse thickening of the glands in one or both breasts, granular, nodular or lumpy, with no clear boundary between the thickened area and the surrounding tissue, tough, elastic and movable. A small number of patients have nipple discharge, which may be clear, milky, yellow, brown or occasionally bloody. There are no enlarged lymph nodes in the axilla.

(2) Ancillary investigations: breast color Doppler ultrasound, X-ray, fine needle aspiration cytology, excision or biopsy of the breast may be useful for diagnosis.

Western diagnostic criteria [9-10]

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1. Breast pain visual analogue pain scale VAS $\geq$ 4 Score.

2. Breast pain duration ≥ 7 days/month.

Differentiated criteria of the depressed liver and Qi obstruction syndrome

The syndrome differentiation and treatment of liver depression and qi stagnation syndrome is carried out by two professors of traditional Chinese medicine (TCM) according to clinical symptoms and signs, pathogens and pathological mechanisms, including local breast pain or swelling, accompanied by emotional depression, fullness in chest and rib cage, thin white tongue coating and string pulse, which meets the standard of liver depression and qi stagnation type in reference [11-12].

Recruitment criteria

The inclusion criteria were as follows:

1. Females between the ages of 18 and 55 who have a substantially regular menstrual cycle and period.
2. Satisfies the diagnostic criteria for the liver-depression-qi-stagnation type of breast pain.
3. VAS pain score ≥ 4 and duration of breast pain ≥ 7 days/month [13-14].
4. Those who have not received medication for breast pain within one month and those who have not been treated with hormonal drugs within six months.
5. Patients who voluntarily participate and sign a written informed consent.

Exclusion criteria

The exclusion criteria were as follows:

1. Patients with non-cyclical breast pain and patients with mild cyclical breast pain.
2. People with pain outside the breast
3. Women during pregnancy, breastfeeding, menopause and in preparation for pregnancy.
4. Allergic persons or persons with a known allergy to the drug or its components. Anyone matching any of the above will be excluded.

Randomization, blinding and intervention

Randomization

MSPM patients were randomized into two groups and randomization was achieved using simple random sampling methods, including the use of IBM SPSS 24.0 software (IBM Corp, Armonk, NY) to generate a table of random numbers. the generated random numbers are sealed in sequentially numbered opaque

envelopes, with each participant's screening sequence number printed on the outside of the envelope and the assigned group name printed on the inside.

The statistician opens the envelope corresponding to the participant's screening sequence number and assigns the participant to the treatment or control group accordingly. As the external manifestations of the **acupoint application** were approximately the same in both groups (smell, appearance), neither the physicians nor the patients themselves were aware of the group to which the patients were assigned. Furthermore, neither the researcher nor the statistician who assessed the results knew the assigned group and was not involved in any aspect of the treatment.

Blinding

As the **DZG** and placebo **acupoint application** are almost identical in appearance and smell, we used a double-blind approach to assess the results and the statisticians were blinded to the study design.

Intervention

A total of 60 patients who met the diagnostic criteria for moderate and severe MSPM were recruited and randomly divided into treatment and placebo control groups (30 for each group). Subjects in both groups received psychological treatment, regular exercise and diet, and maintained a peaceful state of mind.

Treatment group

Mix the Ding tong Gao and Zi Se Xiao Zhong Gao evenly, pass through 100 mesh sieve and reserve; separately weigh honey, vegetable oil and beeswax at 60°C and melt, mix with the above powder, leave at room temperature for 20min, put on the coating machine and press into shape, each piece 0.5g, prepare into Skin-patch of Ding Zi Gao. the treatment group was selected to apply topical Skin-patch of Ding Zi Gao to the local acupuncture points of the breast.

Acupuncture points: Shenque (CV 8), Danzhong (CV 17), Rugen (S18), Wuyi (S 15), Ashi acupoint of breast (for obvious lesions and painful areas), start applying on the 3rd day after the end of menstruation, once a day, hold for 6h each time, 14 times in total, Finished within 1 month.

Control group (placebo group)

Mix honey, vegetable oil and beeswax at 60°C, add caramel and mix thoroughly, add starch, stir for 30min, leave at room temperature for 20min, press and shape to prepare the **placebo acupoint patch**. The selection of acupoints, the method of acupoint application method and the course of treatment are the same as for the treatment group.

(Acupoint application for both treatment and placebo groups were provided by the Institute of Clinical Pharmacy, Beijing Municipal Health Bureau)

Treatment course: All patients were enrolled on the 3rd day after the end of their menstrual period, and were applied once a day, 1 application for 6-8h, 14 times for 1 course of treatment, within 1 menstrual cycle. Follow up at 2 months after the end of the clinical trial.

Acupoint paste usage: Before use, tear off the outer film of the acupoint paste, and then apply the acupuncture point paste to the corresponding acupuncture point.

Ethics permission and registration

The study was conducted in accordance with the standards of the International Coordinating Committee of Global Partnerships and the revised Declaration of Helsinki. Each participant voluntarily signed an informed consent form.

Observation indicators

Primary clinical outcome indicators

1. Onset-Time comparison of pain improvement of the breast in the two groups: VAS < 3 was identified as pain improvement.
2. Change in localized VAS score of the breast: 0 indicates no pain and 10 indicates intolerable pain. The VAS score was evaluated three times a day, and the pain was consistent in each group, and its average value was used as the VAS score of the day. The change of breast pain in each group on day 1,3,5 and 7 was observed.
3. Comparison of patients' mood, sleep, and fullness in both flank before and after treatment.
4. To compare the changes in breast MPQ pain scores before and after treatment in the two groups: four aspects were assessed in terms of pain rating index (PRI), sum of words of pain sensory terms, visual pain score (VAS), and present pain status (PPI).

Secondary outcome indicators

1. Comparison of breast ultrasound imaging scores between the two groups: one assessment from breast gland thickness, duct diameter, and overall breast ultrasound imaging score before and after treatment.
2. Mean VAS pain score pain at 2-month follow-up at the end of treatment in both groups.

Safety evaluation

1. Possible symptoms of skin allergies and other adverse reactions are observed at all times after administration of the drug.

2. General physical examination items (including temperature, resting heart rate, respiration and blood pressure).

The incidence of adverse reactions was used as the main safety evaluation indicator.

Statistical analysis

Data were analysed using SPSS 24.0 software and significant differences between groups were statistically analysed using independent t-tests or non-parametric tests (2 independent sample tests).

Significant differences between the same group before and after treatment were analysed using paired sample t-tests or non-parametric tests (2 correlated sample tests). p-value < 0.05 indicates a statistically significant difference.

Results

General data

A total of 60 patients were recruited and allocated to the treatment and placebo control groups in a 1:1 ratio. A total of 2 patients in the treatment group exfoliated. One patient dropped out of the study due to skin allergy with mild localised skin redness and pruritus at the peri-adhesive area of the acupressure patch, which was not tolerated; the other patient was unable to complete the study due to poor adherence. **Table 1 and Table 2** show the baseline characteristics, medical history and risk factors of the patients compared between the two groups. **Figure 1** shows the recruitment procedure and there were no differences in demographics between any of the groups (p>0.05).

Table 1 Demographic and baseline characteristics.

Item	Treatment group	Control group	p-values
Age (years, mean±SD)	33.33±6.08	34.67±6.93	0.431
weightkg,mean±SD	55.02±7.64	59.11±6.37	0.330
Heightcm	161.13±4.04	162.07±4.81	0.028
BMI (kg/m², mean±SD)	21.21±3.16	22.51±2.33	0.073
VAS	6.38±0.99	6.10±0.93	0.273

Table 2 Comparison of medical history and risk factors between the two groups

Item	Treatment group	Control group	p-values
marital status			
Married	21	20	0.781
unmarried	9	10	
lactation history			
No	11 (36%)	12 (40%)	0.163
Yes	19 (63%)	18 (60%)	
Family history of breast disease			
No	28	27	0.791
Yes	2	3	
Allergic history			
No	23	26	1.00
Yes	7	4	
Acupoint sticking allergy, n (%)			
No	21	18	0.317
Yes	9	12	
History of breast surgery, n (%)			
No	28	25	0.417
Yes	2	5	
Combined with other diseases,n (%)			
No			0.424
Yes	20	25	
	10	5	

Main outcome indicators

Onset-Time comparison of pain improvement of the breast in the two groups

Pain improvement of the target breast in the treatment group occurred earlier than that in the control group with a statistically significant difference ($P < 0.05$), as shown in Fig. 2.

Comparison of the mean changes in breast VAS scores on days 1, 3, 5 and 7 after the end of the medication

After treatment, breast VAS scores decreased in both groups on days 1, 3, 5, and 7; some of the changes were statistically significant ($P < 0.05$). VAS scores decreased in the treatment group compared with the previous time points, and some of them were statistically significant. The treatment group was statistically significant ($P < 0.05$) before and after treatment on days 1, 3 and 5 after the end of treatment compared to the previous time point. There was no statistical significance in the treatment group when comparing VAS scores on day 5 and day 7 after treatment. As shown in **Figure 3**.

Comparison of patients' mood, sleep, and fullness in both flank before and after treatment.

The mood, sleep, and fullness in both flank were significantly improved after treatment in both groups. And the improvement in the treatment group was significantly better than the placebo control group ($P < 0.05$), as shown in **Figure 4**.

compare the changes in breast MPQ scores before and after treatment in the two groups: four aspects were assessed in terms of pain rating index (PRI), sum of words of pain sensory terms, visual pain score (VAS), and present pain status (PPI)

Both control and treated groups showed a significant reduction in breast MPQ pain scores after treatment compared to pre-treatment ($P < 0.05$). The difference between the two groups was statistically significant ($P < 0.01$) as shown in **Table 3**.

Table 3 Comparison of change in breast MPQ score in the two groups

Group	Time	Cases	breast MPQ pain score
Treatment group	before treatment	30	14.63±3.89
	after treatment	30	9.06±2.49*△△
Control group	before treatment	30	15.7±4.45
	after treatment	30	12.64±2.49*

* $P < 0.05$, vs before treatment at the same group; △ $P < 0.05$, △△ $P < 0.01$

vs control group, Statistical significant difference between treatment group and control group.

Comparison of breast ultrasound imaging scores between the two groups: one assessment from breast gland thickness, duct diameter, and overall breast ultrasound imaging score before and after treatment.

The **breast ultrasound imaging scores** were significantly lower in both the treatment and control groups after treatment compared to before treatment ($P < 0.05$). However, the difference between the two groups was not statistically significant, as shown in Table 4.

Table 4 comparison of the average changes of breast ultrasound imaging scores in the two groups.

Group	Time	Cases	breast ultrasound imaging scores
Treatment group	before treatment	30	6.50±2.09
	after treatment	30	5.60±2.19*
Control group	before treatment	30	6.50±2.62
	after treatment	30	5.40±2.54*

* $P < 0.05$, VS before treatment at the same group. there was no statistically significant difference among the two groups ($P > 0.05$)

Mean VAS pain score pain at 2-month follow-up at the end of treatment in both groups

The comparison of the mean VAS pain scores at the 2-month follow-up after treatment between the two groups, $P > 0.05$, was not statistically significant, and it can be concluded that there was no difference between the two groups in terms of the mean VAS pain scores at the 2-month follow-up at the end of treatment. **as shown in Table 5.**

Table 5 Comparison of change in Mean VAS pain score pain at 2-month follow-up at the end of treatment in both groups

Group	Time	Cases	Mean VAS at 2-month follow-up
Treatment group	after treatment	30	5.93±02.37
Control group	after treatment	30	6.66±2.42

* $P < 0.05$, VS after treatment at the different group. there was no statistically significant difference among the two groups ($P > 0.05$).

Safety evaluation

No serious adverse events were observed in either group. Among the 30 patients in the treatment group, 7 patients showed allergy to the peri-acupuncture point adhesive tape, manifested by slightly red local skin and slight itching, with mild severity, accounting for 23.3%.

Among the 30 patients in the placebo group, 4 patients showed allergy to the adhesive tape around the acupuncture point, with the same allergic reaction as the treatment group, and the severity was mild,

accounting for 13.3%; there was no statistical difference between the two groups ($P > 0.05$), as shown in Table 7.

Table 6 Adverse reactions

	Control group	Treatment group
Total adverse effects	7/3	4/30
Skin Itch	5 (16.6%)	4 (13.3%)
Edema	2 (6.6%)	0

Discussion

The incidence of breast pain is increasing every year, and the pathogenesis of **breast hyperplasia** is similar to that of breast cancer. In recent years, the carcinogenic tendency of breast hyperplasia has received increasing attention. Mammary gland hyperplasia (MGH) may increase the risk of breast cancer, according to the Union for International Cancer Control (UICC). In the United States, the incidence of breast cancer in women with MGH is almost twice as high as that in the general female population [15]. The etiology and pathogenesis of breast pain have not yet been fully elucidated.

It is now generally accepted that elevated levels of estrogen secretion lead to upregulation of plasma estradiol concentrations and insufficient secretion of progesterone, which stimulates the mammary epithelial cell response, causing edema, leading to dilation of breast ducts and cyst formation, which in turn causes hyperplasia of breast tissue and leads to breast pain [16, 17]. Hormonal agents (e.g., androgens and progesterone), hormone receptor inhibitors (e.g., tamoxifen) and prolactin inhibitors (e.g., bromocriptine, danazol and iodine preparations) are often chosen as therapeutic agents in Western medicine for the treatment of MGH [18]. However, the side effects of these drugs limit their use in clinical practice.

Recent studies on Chinese medicine for breast hyperplasia have shown fewer side effects and unique advantages. In this study, the clinical efficacy of the treatment group compared with the placebo control group, the VAS score of breast pain, MPQ, was significantly lower in the treatment group ($P < 0.05$), and the score indicated that the **Ding Zi Gao (DZG)** point-application therapy could significantly relieve the clinical symptoms of pain and anxiety and shorten the course of the disease in patients with **moderate to severe Periodic mastalgia (MSPM)**. Patients with moderate or severe breast pain have significant breast pain with increased symptoms, dilated breast ducts, and painful hyperplasia. The external application of Chinese medicine to treat breast hyperplasia mainly focuses on activating blood circulation, relieving pain and reducing swelling. Some studies have shown that the external application of Chinese medicine has obvious efficacy in the treatment of breast hyperplasia, and is more effective in controlling the

symptoms of breast hyperplasia and reducing the recurrence rate. For example, the herbal external elimination of Waixiao Rupī paste has significant effect in reducing the grading of breast pain and shrinking breast lumps in patients with breast pain disorder. [19].

In this study, **Ding Zi Gao (DZG)** was found to be effective in improving pain in patients with breast pain disorder, and the mechanism may be related to the active ingredients of the compound reducing the mammary epithelial cell reaction and decreasing mammary gland edema. **Ding Zi Gao (DZG)** consists of *Lithospermum Erythrorhizon*(Zi cao), *Angelicae Sinensis Radix* (Dang gui), *Carthami Flos* (Hong hua), *Olibanum* (Ru xiang), *Myrrha* (Mo yao). *Lithospermum Erythrorhizon* (Zi cao), is a genus of plants with a bitter-cold taste, originally recorded in Shennong Ben Cao Jing (completed in 1616 AD); it is commonly used in treating acute and chronic inflammation and contains active ingredients of palmitic acid and hexadecenoic acid, which exert their effects on reducing edema and inhibiting inflammatory reactions by inhibiting the increase of capillary permeability and reducing vasodilation [20]. Clinically, alkannin can improve the absorption status of rat small intestine by improving the intestinal wall permeability in the rat ectopic intestinal sac model and improving its absorption by passive diffusion to some extent. [21]. Raw *Radix Rhei Et Rhizome*(Da Huang), which is bitter and cold in nature, was originally recorded in Shennong Ben Cao Jing, and has the ability to remove blood stasis, expel water and relieve pain. Pharmacological studies have shown that the herb and its components have anti-inflammatory and antibacterial effects and inhibit platelet aggregation. In addition, Raw *Radix Rhei Et Rhizome*(Da Huang) with Xuanming powder applied externally can also reduce breast edema in patients with postpartum breast distension, effectively reducing the degree of maternal breast distension and pain ($P < 0.05$), and has the effect of softening and reducing swelling, especially rhubarb has a significant inhibitory effect on the swelling caused by exudates. Clinically, *Radix Rhei Et Rhizome*(Da Huang) is mainly used for the internal and external treatment of acute mastitis, postpartum breast swelling, and mammary gland hyperplasia. [22–25].

In conclusion, the topical application of the **Ding Zi Gao (DZG)** compound has analgesic, anti-inflammatory, anti-swelling and platelet aggregation inhibiting effects on MGH. Among them, the anti-swelling function helps to reduce local glandular tissue swelling. The analgesic effect can effectively relieve pain-induced fear and anxiety. The anticoagulant effect helps to relieve local pain and swelling in addition to preventing thrombosis.

In addition, any effective topical anti-inflammatory drug must enter the dermis and subcutaneous tissues through the skin and then travel through the local blood supply to reach the inflamed tissue, where it exerts its analgesic effects by inhibiting the synthesis of cyclooxygenase (COX) and prostaglandins.

In our study, **Ding Zi Gao (DZG)** was effectively absorbed transdermally and achieved significant clinical results in a short period of time. Definite Violet Cream was found to be effective in improving the symptoms of glandular edema inflammation, including pain and swelling, in patients with MGA, as assessed by different indices and methods, but there was no statistical difference in breast gland thickness and breast nodule university levels between the two groups, indicating that it did not affect the

imaging level of breast ultrasound. The first priority in the clinical management of MGA is to rapidly control the symptoms of painful swelling of the breast. This study shows that **Ding Zi Gao (DZG)** treatment can reduce the VAS pain score of the two groups, and there is a significant difference between the two groups ($P < 0.05$), but there is no significant difference in the VAS pain score of the two groups after 2 months compared with the conventional treatment (control group).

It is known that **Ding Zi Gao (DZG)** treatment can alleviate the short-term efficacy of MGA, but the improvement of the long-term efficacy is not obvious. It can be seen that **Ding Zi Gao (DZG)** can effectively alleviate the local symptoms of patients, but the long-term symptoms are not obvious. Consider the female of breast hyperplasia patients. Progesterone secretion disorder is related to the state. Ultrasound has the characteristics of simple operation, non-invasiveness, flexibility and high sensitivity, so it provides vivid and visual monitoring and evaluation for patients with gout [26]. In this study, the diameter of breast ducts in the two groups under the guidance of breast ultrasound did not change significantly. The reason may be related to the serious condition of the patients with moderate and severe breast pain included in this study. Most of the patients had obvious proliferation and proliferation of breast duct cells and duct dilatation. Therefore, no significant differences were seen in the comparison between the two groups. Compared with the placebo components honey and caramel, the treatment group **Ding Zi Gao (DZG)** contains Vaseline as an auxiliary material, which is more lubricating and irritating, less local water volatilization, and a sharp increase in skin water content, which increases the local drug and skin infiltration, So that the drug is more easily absorbed [27]. Therefore, compared to the placebo group, the treatment group showed significant relief of symptoms and a significant improvement in emotional state.

Due to the small sample size of this study and the close baseline BMI, history and duration levels of breast pain in both groups, the results of this study still require a large sample of randomized, multicenter, controlled clinical trials to explore the principles of action and to unify and standardize the treatment of breast pain in Chinese medicine, and adequate attention should also be given to the adverse effects caused by topical application of Chinese medicine to further confirm the efficacy of **Ding Zi Gao (DZG)** on MGA.

Conclusion

In this work, the skin-patch of **Ding Zi Gao (DZG)** acupoint-application therapy was used for treating **moderate to severe Periodic mastalgia (MSPM)** with Liver depression and Qi stagnation syndrome, showing safe and good clinical effects in terms of quickly alleviating pain and main clinical symptoms as well as inhibiting the mammary gland edema reaction. Furthermore, it decreased the use of NSAIDs, and patients' burden, and enhancing their quality of life.

Abbreviations

DZG: Ding Zi Gao; MPQ: McGill Pain Questionnaire; MSPM: moderate to severe Periodic mastalgia; BMI: Body mass index; VAS: Visual analog scale/score; CSCM: Chinese Society of Traditional Chinese Medicine and Surgery; TCM: traditional Chinese medicine.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Beijing Chinese Medicine Hospital Affiliated to Capital Medical University [Certificate No. **2017BL-034-03**] and registered with the Chinese Clinical Trials Registry. All patients provided written informed consent before enrollment.

Consent to publish

All authors have provided consent for publication of the manuscript in the Journal of Chinese Medicine.

Availability of data and materials

The datasets used in the present study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

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Authors' Contributions

ZDX conceived the study, and SYJ supervised its performance. HQ executed the study, and LH wrote the manuscript. FN and ZYW performed data management and statistical analysis. All authors read and approved the final manuscript.

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Figures

Figure 1

Patient flowchart

Figure 2

Comparison of onset-time of pain improvement of the target breast in two groups. * $P < 0.05$, vs control group, & $P < 0.05$, there was a statistically significant difference ($P < 0.05$)

Figure 3

the changes in the mean VAS scores of patients in the two groups were statistically significant when comparing each group before and after treatment, $*p < 0.05$; the difference between the treatment group and the control group was statistically significant, $&p < 0.05$; compared with the previous time points, the difference between the treatment group before and after treatment was statistically significant on days 1, 3 and 5, $^{\wedge}p < 0.05$;

Figure 4

Comparison of irritable,fullness in both flank and insomnia situation after treatment between the two groups.VS Control*P<0.05