

CLINICAL STUDY

Effectiveness of external Sanjierupi Gao on mastalgia caused by mammary gland hyperplasia: a placebo controlled trial

Yingyi Fan, Xiaohua Pei, Zhaolan Liu, Zhongyuan Xia, Dongxiao Zhang, Afeng Song, Duo Liu

Yingyi Fan, Xiaohua Pei, Surgical Department of the Third Hospital Affiliated to Beijing University of Traditional Chinese Medicine, Beijing 100029, China**Zhaolan Liu**, Centre for Evidence-based Chinese Medicine, Beijing University of Chinese Medicine, Beijing 100029, China**Zhongyuan Xia**, Surgical Department of TCM in Sino-Japanese Friendship Hospital, Beijing 100029, China**Dongxiao Zhang**, Mammary Department of Dongfang Hospital under Beijing University of Traditional Chinese Medicine, Beijing 100078, China**Afeng Song**, Surgical Department of the First Hospital Affiliated to Tianjin University of Traditional Chinese Medicine, Tianjin 300193, China**Duo Liu**, Surgical Department of Hubei Provincial Hospital of Traditional Chinese Medicine, Hubei 430061, China**Supported by** a Demonstrative Project of Research into Specific Therapy and Technology of External Application in Traditional Chinese Medicine; National Sci-Tech Plan of the Ministry of Science and Technology in the 11th 5-Year Plan (2008BAI53B053)**Correspondence to: Prof. Xiaohua Pei**, Third Hospital Affiliated to Beijing University of Traditional Chinese Medicine, Beijing 100029, China. pxh_127@163.com**Telephone:** +86-13911683278**Accepted:** March 4, 2013**Abstract****OBJECTIVE:** To evaluate the curative effect of external application of the Chinese drug, Sanjierupi Gao, on mastalgia caused by mammary gland hyperplasia.**METHODS:** This randomized, double-blinded, and placebo controlled study enrolled 260 patients with mammary gland hyperplasia from five hospitals. Patients were randomly and equally divided in-

to a Sanjierupi Gao treatment group and a placebo control group. An adhesive plaster was applied to the most painful area on either breast for 7 h a day. Treatment lasted for two menstrual cycles without application during menstruation. Mastalgia was used as the main index of curative effect. The change before and after treatment in days of mastalgia, the time to alleviate pain, pain extent, and severe pain scores were observed.

RESULTS: Compared to the control group, the treatment group had significantly fewer days of mastalgia ($P<0.01$), a significantly lower severe pain score ($P<0.01$), and significantly less subjective pain and tenderness ($P<0.05$ and $P<0.01$, respectively). Three days before the follow-up visit, the pain score in the treatment group was significantly lower than that in the control group ($P<0.05$). A non-parametric test was used to compare the time to alleviate mastalgia between the two groups and found no statistical difference ($Z=-0.313$, $P=0.754$).**CONCLUSION:** Application of Sanjierupi Gao can decrease mastalgia duration in patients with mammary gland hyperplasia during menstruation and alleviate the extent of mastalgia. The time to alleviate pain is psychologically influenced.

© 2013 JTCM. All rights reserved.

Key words: Fibrocystic disease of breast; Pain; Treatment outcome; Application therapy**INTRODUCTION**Hyperplasia of mammary glands is characterized by cyclic mastalgia,^{1,2} which often appears or is aggravated

several days before menstruation and often fluctuates with emotional changes.^{3,4}

The treatment of mammary gland hyperplasia aims to alleviate discomfort or pain. Because the mammary glands are close to the body surface, externally applied drugs can be absorbed by the skin and directly alleviate more effectively than orally administered drugs.⁵ However, there is no standardized research into the curative effect of external treatment on mastalgia caused by mammary gland hyperplasia. Additionally, placebos can produce analgesic effects because pain has an extremely strong emotional influence.^{6,7} Therefore, we performed a randomized, double-blind, and placebo controlled study to clinically evaluate the curative effect of external application of the Chinese drug Sanjierupi Gao on mastalgia caused by mammary gland hyperplasia.

METHODS

General data

Two hundred and sixty outpatients with mammary gland hyperplasia from The Third Hospital Affiliated to Beijing University of Traditional Chinese Medicine (TCM), Sino-Japanese Friendship Hospital, Dongfang Hospital under Beijing University of TCM, The First Hospital Affiliated to Tianjin University of TCM, and The Hubei Provincial Hospital of TCM from May 2010 to October 2011 (52 patients from each center) were randomly and equally divided into the treatment and placebo group using computer generated random number sequence. Stratification block randomization methods were used to ensure the balance of participants among centers and between groups. Sealed opaque envelopes were used to conceal the allocation sequence.

Standard of diagnosis

The standard of diagnosis was created in reference to the principles for instructing clinical research into the treatment of hyperplasia of mammary glands with new Chinese drugs⁸ and TCM Surgery (the sixth edition).⁹ Mammary gland hyperplasia can be clinically diagnosed by mastalgia, breast tumors, disturbed or uneven and stronger echo of breast tissues, or cystic dilatation of mammary ducts in color ultrasonography.

Standards of inclusion and exclusion

Standards of inclusion: female patients conforming to the standard for diagnosing hyperplasia of mammary glands were 18-50 years old with a regular menstrual cycle (28 ± 7) days and menstruation. Patients had a visual analogue scale score (VAS) > 3 , moderate pain, cyclic mastalgia before menstruation, and an illness course ≥ 3 months. Patients had not accepted treatment for mammary hyperplasia within one month and had not used hormones within six months. Patients did not have skin lesions or dermatosis and voluntarily accept-

ed the test and gave informed consent.

Standard of exclusion: patients conformed to the standard for diagnosing mammary gland hyperplasia but had no cyclic mastalgia. Patients had breast cancer, inflammation or endocrine diseases. Patients had irregular menstrual cycles or menstruation. Patients had severe primary diseases of the cerebrocardiovascular system, liver, kidney, hematopoietic system, or mental disease. Female patients were pregnant, lactating, in menopause, or preparing to be pregnant. Patients had allergic constitution or were sensitive to the drugs used. Patients were taking part in other clinical tests.

This experiment was approved by the ethics committee of the Third Hospital affiliated to Beijing University of TCM with the approval number 2010007. All patients gave informed consent. This experiment was registered at China Center for registering clinical experiments with the registration number ChiCTR-TRC-12002920.

Therapy

In the treatment group, an adhesive plaster of Sanjierupi Gao was applied to the most painful location on either breast for 7 h a day.

In the control group, a placebo was applied to the most painful place on either breast for 7 h a day.

Sanjierupi Gao and the placebo were produced by Hexiang Pharmaceutical Limited Company (batch number: Z20040073, Heilongjiang, China). The placebo match the Sanjierupi Gao in appearance, color, smell, etc. The two groups were treated for two menstrual cycles without treatment during menstruation. Patients made a follow-up visit for two menstrual cycles to evaluate patients after withdrawal.

Index and method of observation

The patients gave mastalgia scores on the VAS daily. The time calculated by days when VAS score decreased by two was defined as the first length of time to alleviate pain. The days of mastalgia in every menstrual cycle were calculated according to the record of pain. The severe mastalgia score was found according to the patient's record of pain. According to the extent of mastalgia and tenderness in the luteal phase, the researcher divided pain into no pain, mild pain, moderate pain, and severe pain and chose the corresponding pain extent in case report form. According to the record of pain in the two groups, the average pain value was taken from the scores of pain within 3 days before the follow-up visit to reflect the extent of mastalgia during the luteal phase.

Statistical analysis

SAS 6.0 (SAS Institute, Cary, NC, USA) was used to generate random number sequence. SPSS 17.0 (SPSS Inc., Chicago, IL, USA) software was used to do statistical analysis. Completed, rejected, and dropout patients were counted in the five centers. Homogeneous

analysis of baseline values and demography in the two groups was carried out. Measured value (baseline) and the difference among patients at different centers were processed as covariance to deduct the influence of the main index to enhance the efficiency of statistical analysis. To inspect the comparability between the two groups, effective analysis was used to observe indexes of pain. The full analysis set (FAS) and per protocol set (PPS) was reported. $P \leq 0.05$ was considered significant difference. This research is reported according to the detailed list in the statement of Consort 2010 report.¹⁰

RESULTS

Basic patient information and inclusion procedure diagram

Among the 260 patients in the FAS were 130 patients in the treatment group and 130 in the control group. Because of seven dropouts, among the 253 patients in the PPS were 123 patients in the treatment group and 130 in the control group.

The baseline data including age, height, body weight, pulse and respiratory rate, educational level, marital state, reproductive history, breast-feeding history, and familial history were comparable between the two groups ($P > 0.05$).

Comparison of days of mastalgia during menstrual cycles between two groups

For the PPS analysis, the test of normality showed that the data of mastalgia time at various stages in both groups were not normally distributed ($P < 0.01$). A non-parametric test used to compare the difference in mastalgia time at various stages between the two groups showed that the mastalgia time before treatment could be compared ($P > 0.05$) between the two groups. After two courses of treatment, the mastalgia

time in the treatment group was significantly shorter than that in the control group ($P < 0.01$). The results of the FAS analysis were the same as that of the PPS analysis (Table 1).

Comparison of scores of severe mastalgia during menstrual cycle between the two groups

For the PPS analysis, the test of normality showed that the data at various stages in both groups were not normally distributed ($P < 0.01$). A non-parametric test used to compare the scores of severe mastalgia at various stages between the two groups showed that the scores of severe mastalgia before treatment could be compared between the two groups ($P > 0.05$). After one course of treatment, there was no obvious difference in the severe mastalgia scores between the two groups ($P > 0.05$). After two courses of treatment, the severe mastalgia score in the treatment group was significantly lower than that in the control group ($P < 0.01$). The results of the FAS analysis were the same as that of the PPS analysis (Table 2).

Comparison of time to alleviate mastalgia after treatment between the two groups

The time at which the VAS mastalgia score decreased by two was defined as the first time to taking effect. The time to take analgesic effect after treatment was (4 ± 7) days in the treatment group and (4 ± 6) days in the control group. A test of normality showed that the data in both groups were not normally distributed ($P < 0.01$). A non-parametric test used to compare the time to take effect between the two groups showed $Z = -0.313$ and $P = 0.754$, so there was no statistical difference.

Comparison of mastalgia extent between the two groups

A test of normality showed that the data of symptoms at

Table 1 Comparison of days suffering from mastalgia between the Sanjierupi Gao and placebo group

Treatment course	PPS			FAS		
	Treatment group	Control group	<i>P</i>	Treatment group	Control group	<i>P</i>
Before treatment	8±4	8±4	0.556	8±4	8±4	0.570
After one course of treatment	13±9	13±8	0.418	13±8	13±8	0.358
After 2 courses of treatment	11±9	13±8	0.008	11±9	13±8	0.011

Notes: Sanjierupi Gao was applied to the treatment group for 7 h a day. The control group received a placebo treatment. PPS: per protocol analysis; FAS: full analysis set.

Table 2 Comparison of scores of severe mastalgia between the two groups

Treatment course	PPS			FAS		
	Treatment group	Control group	<i>P</i>	Treatment group	Control group	<i>P</i>
Before treatment	6.0±1.2	5.8±1.4	0.183	6.0±1.2	5.8±1.4	0.189
After one course of treatment	5.1±1.7	5.5±1.6	0.054	5.1±1.7	5.5±1.6	0.057
After 2 courses of treatment	3.4±2.1	4.6±2.0	<0.001	3.5±2.1	4.6±2.0	<0.001

Notes: Sanjierupi Gao was applied to the treatment group for 7 h a day. The control group received a placebo treatment. PPS: per protocol analysis; FAS: full analysis set.

various stages were not normally distributed ($P < 0.001$). A non-parametric test used to compare the accumulated scores of symptoms at various stages showed that breast-related symptoms at baseline could be compared ($P > 0.05$). The extent of mastalgia and tenderness in the treatment group was not as great as that in the control group, with statistical difference ($P < 0.05$) after one course of treatment and ($P < 0.01$) after two courses of treatment (Table 3).

Comparison of mastalgia scores during the luteal phase between the two groups 3 days before the follow-up visit

For the PPS analysis, a test of normality showed that the data at various stages in both groups were not normally distributed ($P < 0.01$). A non-parametric test showed that the mastalgia scores in the two groups could be compared 3 days before treatment ($P > 0.05$). The mastalgia score in the treatment group was significantly lower than that in the control group 3 days after one course of treatment and 3 days after two courses of treatment ($P < 0.05$). The results of the FAS analysis were the same as that of the PPS analysis (Table 4).

DISCUSSION

In recent years, research on the external treatment of mammary gland hyperplasia with Chinese medicine has shown promise.^{5,11-15} To popularly use external Chinese drug treatment for mammary gland hyperplasia with, the curative effect and safety must be evaluated through clinically standardized research with large sample sizes at many centers. Sanjierupi Gao, mainly composed of Ezhu (*Rhizoma Curcumae Phaeocaulis*), Jianghuang (*Rhizoma Curcumae Longae*), Jixingzi (*Semen Impatiens*), Tiankuizi (*Radix Semiaquilegiae*), and Baizhi (*Radix Angelicae Formosanae*), can promote circulation

of Qi and blood, remove masses and eliminate swelling. In this study, mastalgia was used as a main index of curative effect. The statistical analysis of mastalgia scores showed that after treatment for two menstrual cycles, there were significantly fewer days of mastalgia during the menstrual cycle in the treatment group than in the control group ($P < 0.01$). Therefore, externally applied drugs could shorten the time of mastalgia.

Statistical analysis showed that after treatment for two menstrual cycles, the severe mastalgia score in the treatment group was significantly lower than that in the control group ($P < 0.01$). Therefore, externally applied drugs could lessen the extent of mastalgia. Moreover, statistical analysis of mastalgia scores in the two groups during the luteal phase 3 days before the follow-up visit showed that after the first treatment course and after the second treatment course, the mastalgia score in the treatment group was significantly lower than that in the control group ($P < 0.05$). Therefore, externally applied drugs could lessen mastalgia, especially during the luteal phase.

We also observed the time to take analgesic effect. According to the recorded mastalgia scores, the time calculated in days when the VAS score decreased by two was defined as the first time to take effect. To exclude the influence of menstruation on mastalgia, patients whose pain score during menstruation decreased by two were rejected. A non-parametric test used to compare the time to take effect on alleviating mastalgia between the two groups showed $Z = -0.313$ and $P = 0.754$ without statistical difference. Therefore, the time to take analgesic effect is psychologically influenced. Moreover, the unreasonable influence of the plan for evaluating the time to take effect on mastalgia pain cannot be excluded. Therefore, the method to evaluate the time to take analgesic effect must be further investigated.

Table 3 Comparison of mastalgia extent between the two groups

Item	Group	Baseline	1 course of treatment	2 courses of treatment
Extent of mastalgia	Treatment group	6.0±1.3	4.0±2.1	2.8±2.1
	Control group	5.9±1.4	4.6±2.2 ^a	4.3±2.2 ^b
Extent of breast tenderness	Treatment group	2.2±0.6	1.4±0.8	1.0±0.7
	Control group	2.1±0.7	1.7±0.8 ^b	1.6±0.9 ^b

Notes: Sanjierupi Gao was applied to the treatment group for 7 h a day. The control group received a placebo treatment. ^a $P < 0.05$ and ^b $P < 0.01$, as compared with the datum in the treatment group.

Table 4 Comparison of mastalgia scores between the two groups 3 days before the follow-up visit

Treatment course	PPS			FAS		
	Treatment group	Control group	<i>P</i>	Treatment group	Control group	<i>P</i>
Before treatment	3.87±2.09	3.83±1.99	0.628	3.92±2.11	3.83±1.99	0.534
1 course of treatment	2.36±2.00	2.99±2.15	0.015	2.37±1.99	3.01±2.14	0.013
2 courses of treatment	2.17±2.01	2.94±2.37	0.017	2.22±2.03	2.97±2.37	0.015

Notes: Sanjierupi Gao was applied to the treatment group for 7 h a day. The control group received a placebo treatment. Two patients dropped out before treatment, two dropped out after one course of treatment and five dropped out after two courses of treatment from the control group. Two patients dropped out from the treatment group. PPS: per protocol analysis; FAS: full analysis set.

REFERENCES

- 1 **Shao XJ**, Chen YX, Yang XY. Observations on curative effect of Hongjinxiaojie capsule on hyperplasia of mammary glands. *Zhong Shan Da Xue Xue Bao (Yi Xue Ke Xue Ban)* 2008; 29(3): 126-127.
- 2 **Li YH**, Wang YW. Observations on curative effect of Ruhexiao on 76 patients with hyperplasia of mammary glands. *Dang Dai Yi Xue* 2012; 18(3): 14-15.
- 3 **Yang MY**, Chen SL. Observations on curative effect of drugs and psychological intervention on hyperplasia of mammary glands. *Zhong Hua Quan Ke Yi Xue* 2010; 8(1): 25-26.
- 4 **Mo XQ**, Liang SH, Li TG. Experience in diagnosing and treating hyperplasia of mammary glands. *Zhong Yi Za Zhi* 2007; 48(2): 112-113.
- 5 **Zhou LJ**, Zhu Y. Research into general condition of externally treating hyperplasia of mammary glands with Chinese drugs in recent years. *Zhong Yi Wai Ke Za Zhi* 2012; 21(6): 50-52.
- 6 **Chen ST**. Progress in research into pre-menstrual syndrome under social, psychological and medical model. *Xian Dai Zhong Xi Yi Jie He Za Zhi* 2003; 12(18): 97-100.
- 7 **Lu Y**, Chen BY. Clinical research into using Rutongling Jiaonang to treat hyperplasia of mammary glands with syndrome of *Qi* stagnation, phlegm accumulation and blood stasis. *Yunnan Zhong Yi Zhong Yao Za Zhi* 2012; 33(5): 15-17.
- 8 Principle for directing clinical research into new Chinese drugs. 3rd ed. Beijing: Health Ministry of the People's Republic of China, 1997: 50.
- 9 **Lu DM**. Surgery of TCM. Shanghai: Science and Technology press, 1997: 91.
- 10 **Kenneth FS**, Douglas GA, David M, the CONSORT Group. CONSORT 2010 statement: report on renewing the guide of parallel, control and randomized clinical experiments. *Zhong Xi Yi Jie He Xue Bao* 2010; 8(7): 604-611.
- 11 **Ying F**, Duan YL. The latest condition of external treatment of hyperplasia of mammary glands with Chinese drugs. *Xinjiang Zhong Yi Yao* 2011; 29(4): 104-107.
- 12 **Tian YH**, Hou JW. Clinical research into external treatment of hyperplasia of mammary glands with Chinese drugs. *Liaoning Zhong Yi Yao Da Xue Xue Bao* 2008; 10(3), 44-45.
- 13 **Zhao ZG**, Sun YP, Wu JS. Progress in research into commonly used external treatment of hyperplasia of mammary glands with Chinese drugs. *Zhong Yi Yao Dao Bao* 2010; 16(4): 114-115.
- 14 **Zhu Q**, Bian WH, Li YG. Progress in research into external treatment of hyperplasia of mammary glands with Chinese drugs. *Zhong Yi Yao Dao Bao* 2011; 17(12): 79-81.
- 15 **Huang M**, Yu QS. Status quo of research into external treatment of hyperplasia of mammary glands with Chinese drugs. *Zhong Yi Yao Lin Chuang Za Zhi* 2012; 24(7): 690-692.