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Research Article

Effects of Kunruning Granules Combined with Milk Ejection on the Inflammatory Factors of Patients with Acute Lactational Mastitis in Early Stage -

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ABSTRACT

Objective: This study explores the effects of Kunruning granules combined with milk ejection on the inflammatory factors of patients with acute lactational mastitis in early stage.

Methods: Patients with acute lactational mastitis in early stage were divided into the observation group and the control group. The observation group received Kunruning granules treatment combined with milk ejection. The control group received traditional antibiotic treatment combined with milk ejection. Recommend rewording for clarity. To evaluate the total clinical efficacy between the groups White Blood Cell count (WBC), C-Reactive Protein (CRP), Procalcitonin (PCT), Interleukin-6 (IL-6), Tumor Necrosis Factor-α (TNF-α) in the blood and (CRP, IL-6 and TNF-α) in the milk were determined before and after the treatment.

Results: Total effective rate of the observation group and the control group were 95.83% and 86%, respectively. The inflammatory factors (WBC, CRP, PCT, IL-6, TNF-α in blood and CRP, IL-6 and TNF-α in milk) after both treatments all decreased obviously when compared with those before the treatments and the above indexes in the observation group after treatment were significantly lower than those in the control group ($p < 0.05$).

Conclusion: Kunruning granules combined with milk ejection method for patients with acute lactational mastitis is safe and effective and the combined treatment method can decrease inflammatory factors levels significantly. In clinical, this treatment can be used as the first choice in treating early stage acute lactational mastitis which can reduce the usage of antibiotics.

Keywords: Kunruning granules; Inflammatory factors; Acute lactational mastitis; Milk ejection method

INTRODUCTION

Acute mastitis is a common inflammatory disease of the breast in postpartum lactating women. Improper feeding method, incorrect feeding posture and lack of nursing experience give rise to milk siltation in the breast duct can cause acute mastitis. Acute mastitis often occurs in the postpartum period of 3 to 4 weeks. Primiparas are at high risk of acute mastitis, and are prone to recurrent attacks during lactation [1]. Acute mastitis has an acute onset with breast clumping, may or may not cause local skin redness swelling and pain, with or without fever, and an increased cell count. *Staphylococcus aureus* is always the pathogenic bacterium. The clinical manifestation of acute mastitis inflammation is intense, and the patients suffer both physically and mentally, which affects the patient life, xtremely easy to induce postpartum depression [2]. At present, it is believed that pathogenic bacteria can be cultured in the milk of lactating mastitis patients, but this will not cause an increased risk of infection in infants, and the benefits of breastfeeding outweigh the risks. In the early stage of acute mastitis, continued breastfeeding can help remove the accumulated milk, reduce local symptoms, and facilitate disease treatment. Therefore, positive prevention and treatment of this disease has important social significance and also plays an important role in the female post-natal recovery and maintenance.

According to statistics, the incidence rate of acute mastitis is 10% - 27% [3]. Most patients will choose to go to the hospital for treatment, and the therapy is often breast physiotherapy plus intravenous antibiotics, where cephalosporin is used as the main antibiotic with quick effect. However, the method could often induce chronic persistent inflammation, resulting in a hard and persistent mass forming galactocele. Galactocele seriously affect the health and the quality of life of both breast-feeding women and their infants [4]. The key in treating breast disease is the early and accurate implementation of treatment. Clinical observations found that Traditional Chinese Medicine (TCM) on early acute lactational mastitis is effective, with the advantages of not affecting normal lactation, and thus gradually accepted by the majority of patients.

In the 1950s, due to the backwardness of China's pharmaceutical industry, the production of drugs could not meet the needs of patients, and hospital preparations came into being. In-hospital preparations are close to the clinic and generally have significant clinical efficacy and unique medicinal value. Kunruning granule is an in-hospital preparation of the Fourth Hospital of Shijiazhuang. It has been used clinically for many years and has a significant effect. TCM in treating diseases is based on the holistic concept and syndrome differentiation, but at present there is no unified and clear standards in clinical practice, so a certain degree of subjectivity and arbitrariness exists. The clarification of the material basis and molecular pathological mechanism in disease occurrence and its prognosis can lay the foundation for helping TCM serve more widely for people all around the world.

A domestic study found that during the detection of pathogens in lactating acute mastitis females, no pathogenic bacteria was found in half of the patients [5]. However, in a foreign study on healthy breastfeeding women, it was using shown that nearly one-third of the subjects were detected with high-load pathogenic bacteria infection [6]. Acute mastitis in lactation is no longer a simple infectious disease as generally considered, and its susceptibility and severity are not related to the number of pathogenic bacteria infected [7], but positively correlated with the levels of inflammatory factors in both serum and milk [8]. Studies have shown that IL-6 and TNF-α are important inflammatory cytokines in acute mastitis [9]. WBC, CRP and other traditional infection monitoring indicators have been widely used in the clinical works, but they are affected by many factors. Some studies showed that, based on PCT, the combined application of CRP mode was more effective in diagnosis [10]. In this study, the effect of Kunruning granules on acute lactational mastitis was investigated by the changes of acute inflammatory factors.

Information and Methods Clinical data

Patients with acute lactational mastitis were recruited from the Department of Traditional Chinese Medicine of the Fourth Hospital of Shijiazhuang from June 2018 to June 2019. All patients gave gave their written informed consent prior to participating in the study. They all met the western medicine diagnostic criteria for mastitis and were identified at the early stage of acute mastitis. With reference to the diagnostic criteria of "acute mastitis" in *Western Medical Surgery* [11] it was protocolled as follows: (1) the patient has breast pain on one or both sides, the milk is not discharged smoothly, and no pus is formed; (2) the patients breast is with pressing pain and palpable lumps, skin reddish or not, and enlarged lymph nodes could be found in the axillary side of the affected side; (3) probably accompanied by high fever, chills, and accelerated pulse; (4) WBC count and CRP in peripheral blood are normal or elevated. The patients included in the study also met the syndrome differentiation type of TCM and belonged to the "Qi stagnation fever type", according to the diagnostic criteria for early postpartum mastitis in the *Chinese Medicine Surgery* and *Guiding Principles for Clinical Research of* New Chinese Medicine (Trial) [12,13]. Color Doppler ultrasound only indicated acute mastitis without abscess formation. Informed consent was obtained from and signed by the patients and their family members, and this research was approved by the hospital ethics committee. Patients included in the study were randomly divided into 2 groups. The patients did not use other drugs for acute mastitis during the entire treatment period. There were 48 patients in the observation group with the oldest 36 years old, the youngest 20 years old and an average age of 28.3 ± 1.7 years old; all patients were primiparas, and the course of disease did not exceed 3 days. There were 50 patients in the control group with the oldest 37 years old the youngest 18 years old, and an average age of 27.6 ± 1.9 years old. Their course of disease did not exceed 3 days. Women with abnormal nipples, e.g. crater nipples and flat nipples, were not included in the study. There was no significant difference in general information between the two groups ($p > 0.05$), and thus they were comparable for this study.

Treatment

All patients received basic interventions for breast massage. The control group was routinely given 8 million units of penicillin intravenously, twice per day, and the observation group was treated with Kunruning granules, 30 g doses, twice per day. The basic ingredients of Kunruning: *Prunellae spica*, *Bupleuri radix*, *Toosendad fructus, Trichosanthis fructus, Sargassum, Spatholobi caulis, Gleditsiae spina, Melanteritum, Salviae Miltiorrhizae Radix et Rhizoma, Moutan cortex, Citrus Reticulatae Pericarpium Viride, Taraxaci herba, Phragmitis rhizoma, Paeoniae Radix Rubra, Cinnamomi ramulus.* For patients with high fever, 15 g plaster *Gypsum fibrosum* was added. The appearance and thin-film microscopic identification and empirical identification of the Chinese herbal decoction pieces used in the experiment all conformed to the requirements of the Chinese Pharmacopoeia 2015 edition. Meanwhile, both groups of patients were instructed to take a bland diet and rest well. Breast massage was performed by professional medical staff in our hospital. The lumps of the breasts had hot compresses applied. Knead in the direction of the breast collaterals to empty the milk and the lumps were kneaded until they turned soft. The treatment effect of the two groups was observed once a day.

TCM syndrome scores

Refer to the Loue's scoring method [14], which includes local skin redness, swelling, fervescence, and pain. Each item is divided into 4 levels. According to the severity of the symptoms, 1 to 4 points are recorded. Finally, the scores are summarized.

Curative effect

Clinical signs and symptoms: Record the time when body temperature returns to normal, the time of skin redness, swelling, heat, pain to be subsided, the time of lactogenesis, and the effective rate of treatment for the disease.

Laboratory indicators: The blood routine, CRP, PCT, IL-6, TNF-α in the serum, and CRP, IL-6, TNF-α in the milk were measured before and after treatment in the two groups of patients.

Criteria for therapeutic effect: Protocolled with reference to *the* Clinical Guiding Principles of New Chinese Medicines · Clinical Guiding Principles of New Chinese Medicines for the Treatment of Early Acute Mastitis Sickness (Acute Mastitis) [13].

Cured: Local symptoms (redness, swelling and pain in the breast) and systemic symptoms completely disappeared, the total number of leukocytes and neutrophils are normal or nearly normal, and the efficacy index was ≥ 90%;

Improved: Local and systemic symptoms significantly reduce and the clumps shrink; the total number of blood routine leukocytes and neutrophils are significantly reduced and the efficacy index is between 70% to 89%;

Effective: Systemic symptoms, local swelling and pain, and clumps are reduced, the total numbers of blood routine leukocytes and neutrophils are significantly reduced, and the efficacy index is between 30% to 69%;

Failed: Local and systemic symptoms are not significantly improved or even worsened, blood leukocytes and neutrophils are not reduced or the efficacy index is < 30%.

Effectiveness = Cured + Improved + EffectiveStatistics

The SPSS 22.0 software package was used for statistical analysis and processing. Normally distributed measurement data were presented as mean ± standard deviation (x ± SD). For measurement data that were normally distributed (or approximately normally distributed) with homogeneous variances, paired-sample *t*-test was used for interclass omparisons of the pre-treatment and post-treatment values, whereas independent-sample *t*-test was used for interblock comparison. Data with skewed distribution were assessed using nonparametric rank-sum test. With respect to the evaluation criteria, $\alpha = 0.05$ and $p < 0.05$ were used as the threshold for statistical significance.

RESULTS

Comparison of total therapeutic effect

The total effective rate was 95.83% in the observation group and 86.00% in the control group and the difference between the two groups was statistically significant, indicating that the therapeutic effects were better in the observation group than those in the control group (Table 1).**Comparison of therapeutic effect on TCM syndrome**

The TCM syndrome scores in the two groups after treatments were significantly lower than those collected before treatments ($p < 0.05$). The TCM syndrome scores in the observation group were significantly lower than those in the control group also with significant difference ($p < 0.05$) (Table 2).

Comparison of symptom scores between the two groups

After treatment, the local breast redness, swelling, heat and pain, the body temperature returned to normal, and the time of lactogenesis was significantly shorter than that in the control group, and the difference was statistically significant ($p < 0.05$) (Table 3).

Serum inflammatory factor levels in both groups

Serum WBC, CRP, PCT, IL-6, and TNF-α levels in the two groups were significantly lower than those collected before treatment (p <

Table 1: Comparison of therapeutic effects between the two groups (case/%).

Groups	Patients (n)	Cured	Improved	Effect	Failed	Effectiveness
Observation	48	38(79.17)	5(10.42)	3(6.25)	2(4.17)	46)95.83)$^{\#}$
Control	50	32(64.00)	7(14.00)	4(8.00)	7(16.00)	43(86.00)

Note: Inter-group comparison, $^{\#}p < 0.05$. The difference between the two groups was statistically significant, indicating that the therapeutic effects were better in the observation group than those in the control group.

Table 2: Comparison of TCM syndrome scores before and after treatment (x ± SD).

Groups	Patients (n)	Time	TCM syndrome scores
Observation	48	Before Treatment	13.52 ± 4.46
		After Treatment	02.02 ± 0.85$^{*\#}$
Control	50	Before Treatment	13.58 ± 4.52
		After Treatment	05.32 ± 1.92*

Note: Intra-group comparison, $^{*}p < 0.05$; inter-group comparison, $^{\#}p < 0.05$. The TCM syndrome scores in the two groups after treatments were significantly lower than those collected before treatments. The TCM syndrome scores in the observation group were significantly lower than those in the control group also with significant difference.

Table 3: Relevant clinical symptoms recovery time and lactation time (d, x ± S).

Groups	Patients (n)	Breast Swelling Time	Body temperature recovery time	Mass disappearance time	Lactation time
Observation	48	2.29 ± 0.92$^{\#}$	1.53 ± 0.72$^{\#}$	2.55 ± 0.96$^{\#}$	1.89 ± 0.66$^{\#}$
Control	50	3.37 ± 0.88	2.43 ± 0.65	4.28 ± 1.39	2.35 ± 0.85

Note: Intra-group comparison, $^{*}p < 0.05$; inter-group comparison, $^{\#}p < 0.05$. After treatment, the local breast redness, swelling, heat pain subsided, the body temperature returned to normal, and the time of lactogenesis was significantly shorter than that in the control group, and the difference was statistically significant.

0.05), and serum WBC, CRP, PCT, IL-6, and TNF-α levels in the observation group were significantly lower than those observed in the control group ($p < 0.05$) (Table 4).

Milk inflammatory factor levels in both groups

After treatment, the levels of CRP, IL-6, and TNF-αin the milk of the two groups were significantly lower than those before treatment ($p < 0.05$). The Milk CRP, IL-6, and TNF-α levels in the observation group were significantly lower than those in the control group ($p <$ 0.05) (Table 5).

DISCUSSION

Acute mastitis is a common clinical disease occurring in lactating women. It is "an inflammatory state of breast tissue with or without infection" [11]. Body immunity of primiparas, decreases after childbirth and they are prone to get infection. Clinically, acute mastitis can occur at any stage of lactation [15]. Acute mastitis affects normal breastfeeding of the mother, and even leads to delactation of the mother during the puerperium, causing psychological and physiological impacts on both mothers and their newborn babies. At present, antibiotic systemic treatment is a commonly used therapy for acute mastitis. Although this method can quickly control the infection, it cannot comprehensively regulate the systemic inflammatory response, and even leads to acute mastitis complicated with breast cysts [4]. Although some drugs clearly do not affect breastfeeding per their instructions, there are reports in literature that antibiotics are excreted with milk [16]. Breastfeeding women often consider the effects of drugs on their milk and are skeptical of continuing to breastfeed after using antibiotics. In the Guidelines for the Clinical Application of Antibacterial Drugs issued by the Ministry of Health of the People's Republic of China in 2004, it is clearly stated that breastfeeding females should suspend breastfeeding when using any antibacterial drug; the use of antibiotics and suspension of breastfeeding will both affect mothers and children [17]. With the widespread use and abuse of antibacterial drugs, problems such as bacterial resistance and secondary infections [18,19] have become prominent. Therefore, it is urgent to find safe and effective substitutive therapies in treating acute mastitis.

Acute mastitis belongs to the category of "breast carbuncle". The Women's Congress Complete Recipes refers to "women's breast carbuncle, which is agglomerated by milk, thin and smooth in skin, and finally forms a crust" [20]. Milk stasis, Qi stagnation of liver or stomach heat stasis, exogenous pathogens invasion are the pathogenesis of this disease. Milk stasis causes Qi and blood stasis, obstruction of the breast collaterals, and milk stasis, which leads to the occurrence of the disease [8]. Nipples belong to the Foot Jue Yin Liver Meridian and the breasts belong to the Foot Yang Ming Stomach Meridian. The principle of TCM for treating acute mastitis are to clear the liver and relieve the stomach, to relieve Qi and stagnation, to dredge the channels and collaterals, to remove blood stasis, and to clear the heat and toxicity. *Taraxaci Herba*, which belongs to the liver and stomach meridians, has the functions of clearing heat and detoxifying, reducing swelling, and dissolving clumps, and is an essential medicine in treating acute mastitis. The *Trichosanthis Fructus* can soothe the stagnation, warm the meridian and promote lactation, and always used together with *Taraxaci Herba* as the monarch drugs in treating the early stage of acute mastitis caused by heat-toxicity. *Bupleuri Radix* belongs to the liver meridian, which has the effects of antipyretics and it can dredge the liver and relieve depression. It is an essential medicine for treating

Table 4: Comparison of indexes of serum inflammation factors (x ± S).

Groups	Patients (*n*)	Time	WBC/10⁹•L⁻¹	CRP/mg•L⁻¹	PCT/ng•ml⁻¹	IL-6/pg•ml⁻¹	TNF-α/ng•L⁻¹
Observation	48	Before Treatment	13.52 ± 4.46	42.05 ± 13.66	2.56 ± 0.78	122.23 ± 12.05	192.03 ± 25.48
		After Treatment	06.02 ± 1.85*#	06.52 ± 1.68*#	0.18 ± 0.03*#	048.68 ± 9.56*#	098.65 ± 16.85*#
Control	50	Before Treatment	13.58 ± 4.52	42.55 ± 14.08	2.48 ± 0.69	128.52 ± 18.32	194.96 ± 28.53
		After Treatment	09.22 ± 2.92*	12.82 ± 1.72*	0.44 ± 0.05*	084.32 ± 10.58*	142.35 ± 19.06*

Note: Intra-group comparison, *$p < 0.05$; inter-group comparison, #$p < 0.05$. Serum inflammation factors levels in the two groups were significantly lower than those collected before treatment, and in the observation group were significantly lower than those observed in the control group.

Table 5: Comparison of indexes of milk inflammation factors (x ± SD).

Groups	Patients (*n*)	Time	CRP/mg•L⁻¹	IL-6/pg•ml⁻¹	TNF-α/ng•L⁻¹
Observation	48	Before Treatment	40.63 ± 9.25	118.68 ± 11.25	188.03 ± 24.56
		After Treatment	06.05 ± 2.02*#	049.85 ± 10.42*#	096.73 ± 16.84*#
Control	50	Before Treatment	41.36 ± 9.95	122.36 ± 18.22	188.92 ± 29.54
		After Treatment	10.26 ± 4.52*	078.58 ± 11.58*	138.53 ± 18.76*

Note: Intra-group comparison, *$p < 0.05$; inter-group comparison, #$p < 0.05$. After treatment, the levels of inflammation factors in milk of the two groups were significantly lower than those before treatment. The milk inflammation factors in the observation group were significantly lower than those in the control group.

liver Qi stagnation. Vinegar preparation can elevate the it's effect of soothing liver and regulating Qi, and it serves as the ministerial drug. Vinegar processed *Citrus Reticulata Blanco* can *Toosendad Fructus* can work together with *Bupleuri Radix* to relieve liver and regulate Qi. When Qi is unblocked the milk is also unhindered; *Melanteritum*, *Salviae Miltiorrhizae Radix et Rhizoma* , *Moutan Cortex*, *Paeoniae Radix Rubra* can be used to stimulate Qi, circulate blood, and tonify the liver meridian. *Prunellae Spica*, *Sargassum* belongs to the liver meridian, and they can clear the liver-fire and disperse swelling. So they are used in treating breast disease caused by liver Qi stagnation; *Phragmitis Rhizoma* clears heat and cools blood; the 10 above mentioned drugs work together as adjuvant drugs. *Cinnamomi Ramulus*, warm-natured, can protect against heavy cold caused by *Taraxaci Herba* and *Phragmitis Rhizoma*, serving as the conductant drug. The combination of all above medicines has the comprehensive effects in dredging the live, regulating Qi, promoting blood circulation, removing blood stasis, eliminating symptoms, clearing heat and detoxifying. The results of this experimental study showed that compared with antibiotic treatment, Kunruning granules treatment combined with breast massage can significantly reduce the levels of serum WBC, CRP, PCT, IL-6 and TNF-α levels as well as CRP, IL-6 and TNF-α levels in milk. This is obviously related to the anti-inflammatory components in TCM. Modern pharmacological research shows that its main ingredients-*Taraxaci Herba* [21,22], *Trichosanthis Fructus* [23], *Bupleuri Radix* [24] have obvious anti-inflammatory and antibacterial behaviors, *Trichosanthis Fructus* also has the effect of improving the body's immunity [25]; the other ingredients also have different degrees of anti-inflammatory and antibacterial activities.

The symptoms of redness, swelling and pain in patients with acute mastitis are the results of innate immune response. Nuclear factor-κ B (NF-κ B) immune signaling pathway plays an important role in the local and systemic inflammatory response of lactating mastitis [26]. Milk silting-up is the most common cause of lactating mastitis [27]. The silted milk causes mechanical damage to the body, produces a large amount of stimulating factor-DAMPs molecules, and activates the TLR-mediated NF signaling pathway [28]. At the same time, lactic acid produced by the silted milk also activates the TLR-mediated NF-κ B signaling pathway [29]. Stimulating factors activate the NF-κ B signaling pathway to regulate the expression of various inflammatory factors, i.e. CRP, IL-6, TNF-α and other inflammatory factors and release of these inflammatory factors can further activate the NF-κ B signaling pathway [30], continuing the complex loop of the inflammatory response, leading to the constant amplification of the initial inflammatory signal. Patients with acute mastitis have significantly increased levels of inflammatory factors such as CRP, IL-6, TNF-α in serum and milk [31,32], and the expression level of inflammatory factors is closely related to the severity of the symptoms of acute mastitis. TNF-α can promote the activation and aggregation of leukocytes, enhance their phagocytic capability and their adhesion with endothelial cells, and TNF-α has high specificity, and it is the primary factor of inflammatory response. IL-6 plays a synergistic role in regulating the occurrence of inflammatory reactions and has an intrinsic anti-inflammatory effect. The levels of IL-6 in serum and milk significantly increase during acute mastitis [31]. IL-6 increases and plays a role in the early stages of acute mastitis, activates multiple inflammatory response signal pathways, and the NF-κ B cascade to reduce protein synthesis in milk [33]. IL-6 can also promote the production of CRP and participate in the inflammatory response, immune regulation and other effects of the body. CRP is a non-specific marker of inflammatory diseases and infections, which sharply increases when the disease happens and quickly return to normal when the disease is relieved. In clinical, it is a very sensitive indicator of the acute phase [31,32]. During inflammatory stimulation, the serum PCT level will increase significantly in 2 to 6 h and reach peak in 6 to 24 h. Generally, it will not increase for viral infections, which can help clinicians judge the necessity of antibiotics usage [33]. In this study, the levels of serum and milk inflammatory factors were significantly reduced in the two groups after treatment. The patients in the observation group who used the TCM-Kunruning granules had a more significant decrease. This showed that western medicine can control infections in acute mastitis, while the usage of TCM is more effective in balancing the systemic inflammatory response, improving systemic and local breast symptoms, and promoting the recovery of lactation, which is of special meaning to the lactating women and their infants.

The production and development of TRM theory are inseparable from the clinical practice of traditional Chinese medicine. The clinical usage and dosage of TRM also come from clinical practice. Kunruning granules have been used in our hospital for many years, and its clinical safety and effectiveness have been fully certified. With the development of in vivo drug analysis technology, the in vivo exposure to Chinese herbal medicine will be improved day by day, and new research methods for traditional Chinese herbal medicine will be added to clarify the effectiveness, safety and mechanism of action of this therapy.

By systematically retrieving domestic and foreign literature from Jan 1980 to Mar 2020, reports on the adverse reactions/events caused by traditional Chinese medicine application for lactating women were collected and collated. Then, retrospective research and statistical methods were applied for analyzing the adverse reactions of traditional Chinese medicine to lactating women and the situations of their infants, whereas no relevant reports were found about the ingredients used in our formula. However, further exploration of the clinical pharmacology and toxicology of these compounds should be carried out, so as to provide references for effectively guiding the safe and rational drug use in the clinic.

In conclusion, Kunruning granules have been used for many years in treating the early stage of acute lactational mastitis, and no adverse reaction has ever occurred. This TCM is safe and provides a good choice to treat early lactating acute mastitis.

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