

Effects of external application of compound Qingbi granules on acute gouty arthritis with dampness-heat syndrome: A randomized control trial

Shuang Ren

China Medical University

Fanyan Meng

China Medical University

Yantong Liu

China Medical University Hospital

Yun Meng

China Medical University Hospital

Ning Tao

China Medical University Hospital

Ruoshi Liu

china medical university

Jie Zhang (✉ zhangjie945@hotmail.com)

China Medical University Hospital

Research

Keywords: Acute gouty arthritis therapy, External application of Traditional Chinese Medicine, regulation of inflammatory response, therapeutic effects

Posted Date: July 6th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-39352/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published on November 7th, 2020. See the published version at <https://doi.org/10.1186/s13020-020-00398-8>.

Abstract

Background

The use of anti-inflammatory and analgesic drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) for treating acute gout has limitations, such as a high incidence of adverse reactions in the gastrointestinal tract and toxicity in the liver, kidney, and heart. Hence, a new safe and effective treatment approach to reduce the use of anti-inflammatory and analgesic drugs, incidence of adverse reaction, and patients' burden needs to be explored. This randomized controlled clinical trial investigated the clinical efficacy and safety of external application of compound Qingbi granules (CQBG) in treating acute gouty arthritis, providing evidence for designing a safe and effective optimization protocol of acute gouty arthritis (AGA) comprehensive treatment.

Methods

A total of 90 patients in line with the diagnostic standard of AGA were recruited and divided randomly into control, T1, and T2 groups (30 in each group). Participants in three groups all received Western-medicine-bastic treatment (low-purine diet, drinking water more than 2000 mL/d, oral loxoprofen, and NaHCO_3). Besides, the T1 group received an external application of diclofenac diethylamine emulgel, while the T2 group received an external application of CQBG. Participants in control group were treated by single-use Western-medicine-bastic treatment. With a treatment course of 7 days and a follow-up for subsequent 7 days, the three groups were compared in terms of primary outcome indicators including swelling, pain improvement, and change in pain duration and secondary outcome indicators including serum C-reactive protein (CRP), uric acid (UA), and change in thickness of the inflammatory synovium of joints under ultrasound. Meanwhile, the safety of the protocol was evaluated.

Results

The three groups of patients had no obvious differences in age, body mass index, history of gout, complication, and so on before recruitment. A comparison between pretreatment and post-treatment revealed remarkable reductions in the arthralgia VAS score and the swelling score in the three groups after the treatment and the improvements in the T2 group were more obvious than those in the T1 and control groups ($P < 0.05$). Regarding onset-time of pain improvement and pain duration, the T2 group had more significant efficacy compared with the other two groups ($P < 0.05$). The serum CRP and blood UA levels in the three groups significantly decreased after the treatment, but with no significant inter-group difference. The improvement in thickness of the inflammatory synovium in joints tested by ultrasound was more significant in the T2 group than in the control group ($P < 0.05$). For safety evaluations, no significant difference in the incidence of adverse events was found.

Conclusions

The external application of CQBG combined with Western–medicine–basic treatment in patients with AGA improved arthralgia and swelling, shortened the period of taking NSAIDs, and reduced the levels of CRP and serum UA. Its therapeutic effect was significantly better than the effect of single-use Western medicine basic treatment and additive diclofenac diethylamine emulgel. The study provided evidence for the clinical application of CQBG combined with Western medicine in treating AGA.

Trial registration:

ChiCTR, ChiCTR1800018020. Registered 27 August 2018, <http://www.chictr.org.cn/showproj.aspx?proj=27138>

1. Background

Acute gouty arthritis (AGA) is clinically characterized by severe arthralgia, redness and swelling of joints, and restricted movement. Patients often go to see a doctor with unbearable arthralgia as the primary cause, which seriously impacts the quality of life and social functioning of patients due to its easy relapse and difficult cure [1]. With the change in modern diet structure, the incidence of gout in China continues to increase every year; it is 8.6% in men [2] and more common in young individuals, hence gaining increasing attention in the clinic. The priority in the clinical treatment of AGA is to quickly control the acute inflammatory reaction and reduce arthralgia. Common drugs can be divided into three types [3]. Colchicine, as a typical drug in the first type, rapidly relieves pain through inhibiting inflammatory reactions. However, its therapeutic dose is similar to the toxic dose, which causes common gastrointestinal reactions such as nausea, vomiting, diarrhea, and stomachache. Besides, it leads to damage in the liver and kidney and myelosuppression, causing limitations in the clinical application. The second type comprises nonsteroidal anti-inflammatory drugs (NSAIDs), the first-line drugs in treating gouty arthritis. They act mainly by suppressing epoxidase and reducing the generation of arachidonic acid metabolites (prostaglandin) to play a role in anti-inflammation, antipyretic, and analgesia. Common adverse reactions of this drug are peptic ulcer, gastrointestinal perforation, upper gastrointestinal hemorrhage, and so forth. The impairment of kidney function of this drug limits its use in patients accompanied by gouty nephropathy that is the common complication of gout. Meanwhile, the risk of cardiovascular and cerebrovascular diseases also limits its use in patients with cardiovascular and cerebrovascular complications. Glucocorticoid drugs, the third type, hinders the development of gouty arthritis by suppressing immunoreactions. It can cause complications such as gastrointestinal ulcer, hypertension, diabetes, and osteoporosis and relapses easily after stopping. Therefore, it is not suitable for long-term use. Hence, it is urgent to seek a novel effective complementary therapy that has less toxic (side) effects while improving arthralgia and swelling during acute attacks and recovering joint function.

Studies on AGA treatment with traditional Chinese medicine based on syndrome differentiation have provided different drugs for different syndromes, showing good clinical efficacy and fewer side effects and thus receiving increasing attention [4]. The syndrome of dampness and heat in traditional Chinese medicine is mostly common in the acute stage of gouty arthritis. The traditional Chinese medicine for clearing heat and removing dampness through oral administration, such as Simiao Powder formula [5], Zhuye Shigao decoction [6], and Gout decoction [7], has significant effects in terms of improving inflammatory symptoms in patients with gout and levels of inflammatory markers [C-reactive protein (CRP)], blood uric acid (UA) level]. Meanwhile, an animal study [8] showed that Simiao Powder significantly suppressed the expression of inflammatory cytokines IL-6, TNF- α , and IL-1 β and decreased the levels of caspase-1 and ASC mRNA in NLRP3 and TLR4–NF- κ B pathways in the joint of rats with AGA. Intragastric administration of Gout decoction [9] significantly decreased the number of urate crystals in the joints of rats with AGA, improved swelling in the involved joints, and inhibited the secretion of inflammatory cytokines such as IL-1 β and TNF- α in joints. There were few such studies on the external application of traditional Chinese medicine in the treatment of AGA and the existing researches were lack of standardization. Clinically, the external application of traditional Chinese medicine is an important administration mode with a long history, which has been recorded in multiple Chinese medicine classics and has clear therapeutic efficacy. It provides a proper approach for patients inconvenient with oral administration and the dose of the drug administered percutaneously is relatively small. Recent studies suggested that the working mechanism underlying the external application of traditional Chinese medicine might have a correlation with its local microabsorption and microstimulation, further improving local microcirculation, promoting inflammatory absorption, alleviating tissue adhesion, and participating in the overall regulation of the balance of nerve–endocrine–immune network [10].

Based on the characteristics of syndrome differentiation and treatment in Chinese medicine combined with the advantages of external treatment, CQBG was developed to treat the syndrome of heat and dampness of AGA, using *Cortex Phellodendri* and *Herba tuberculata speranskia* as the main components. *Cortex Phellodendri* has a cold nature, while *Herba tuberculata speranskia* has a warm nature. In Chinese medicine theories, “warm can neutralize damp while cold can resolve heat”; therefore, the two drugs were used together to realize specific therapeutic effects on syndromes in patients with dampness-heat syndrome. *Cortex Phellodendri* is bitter with alkaloids such as berberine, lipid, and sterol as the main medicinal components. They have anti-inflammatory, antibacterial, and antigout effects; participates in cell immunoregulation; and suppresses apoptosis in articular chondrocytes[11]. The main ingredients of *Herba tuberculata speranskia* are kaempferol, quercetin, ferulic acid, and so forth. The external emulsion mainly comprising *Herba tuberculata speranskia* has good anti-inflammatory and analgesic effects on arthralgia and soft tissue injuries [12, 13]. Previous clinical observations indicated that the external application of CQBG could quickly alleviate arthralgia in patients with osteoarthritis with dampness-heat syndrome, improve arthrocele, and eliminate discomforts such as motion limitation, helping patients relieve their symptoms and recover social functions. In addition, the external application avoided clinical limitations such as liver and kidney toxicity caused by oral drugs.

This study adopted a randomized, controlled, and follow-up research protocol and combined with ultrasound to compare the change in inflammatory indicators in patients and assess the efficacy and safety of CQBG-based combination therapy on AGA, so as to obtain the clinical and safety evidence of CQBG combined with Western-medicine-bastic treatment in improving AGA arthralgia and swelling in a standardized manner.

2. Materials And Methods

2.1 Research design

This trial was designed as an open-label, randomized, controlled, and parallel-group study that focused on the therapeutic efficacy and safety of CQBG combined with Western-medicine-basic treatment in treating AGA. It was conducted in the Department of TCM, the First Affiliated Hospital of China Medical University, from September 2018 to December 2019. The study was approved by the ethics committee of the First Affiliated Hospital of China Medical University and registered in the Chinese Clinical Trial Registry. All patients signed the informed consent form.

2.2 Diagnostic criteria

2.2.1 Diagnostic criteria of AGA

For the diagnosis of primary gout, one can refer to the gout classification criteria in the 2015 American College of Rheumatology (ACR)/European League Against Rheumatism(ULAR) [14].

Acute attack stage of gout: Signs may not occur before the attack. Typical patients with the acute attack are often awakened by arthralgia, which worsens progressively and reaches the pain peak about 12 h later, with unbearable bursting pain, cutting pain, and gnawing pain. The involved joints present swelling, burning, tight skin, obvious tenderness, and restricted motion. It can voluntarily alleviate and return to normal in a few days (up to 2 weeks). The first attack often involves a single joint, with more than 50% in the first metatarsophalangeal joint and 90% in the later course. Besides, joints such as dorsum pedis, heel, ankle, and knees can be involved. Symptoms such as fever, chill, headache, palpitation, and nausea can occur in some patients with an increased number of white blood cells, CRP level, and erythrocyte sedimentation rate, showing urate crystals in ultrasound.

Hyperuricemia: twice test of blood UA levels on different days: sUA > 420 mmol/L.

2.2.2 Diagnostic criteria of traditional Chinese medicine

For dampness-heat syndrome, one can refer to *Diagnosis and Treatment in Chinese Medicine of Zhuoyubi (gouty arthritis)* published by the State Administration of Traditional Chinese Medicine Office (2017 edition).

The disease progresses rapidly with swelling, heat pain, and severe pain in local joints, often involving single or multiple joints and accompanied by fever, fear of cold, thirst, anxiety, headache, sweating, less and yellow urination, red tongue, yellow or greasy tongue coating, and stringy and rapid pulse.

2.2.3 Recruitment criteria

The participants should meet all the following conditions:

(1) conforming to the diagnostic criteria of AGA and hyperuricemia; (2) diagnosis of dampness-heat syndrome in traditional Chinese medicine; (3) age 18–70 years and any sex; (4) AGA attacks ≥ 1 in the last year; (5) alleviation period in previous AGA attacks, ≤ 14 days; (6) main observation parts including first metatarsophalangeal joint, dorsum pedis, ankle joint, knee joint, and so forth, and every participant allowed to have only the most severe joint (target joint) observed and recorded, with no change during the observation; (7) VAS score (evaluation of pain scoring criteria) in the target joint, ≥ 3 ; (8) < 72 h between the last treatment and the attack; and (9) patients who voluntarily participated and signed the written informed consent form.

2.2.4 Exclusion criteria

Participants having one of the following conditions should be excluded:

(1) Secondary gout or arthropathy caused by other diseases (e.g., rheumatic arthritis, pyogenic arthritis, traumatic arthritis, senile osteoarthritis, pseudogout, chemotherapy, radiotherapy, chronic lead poisoning, and acute obstructive nephropathy)

(2) Under chronic gout intermittent period or having chronic tophaceous gout

(3) More than four joints involved in the AGA attack

(4) Patients taking drugs that affected the metabolism of blood UA, for example hydrochlorothiazide, furosemide, low-dose aspirin, and drugs that contained the aforementioned components, such as compound reserpine and hydrochlorothiazide; or stop taking glucocorticoids less than one month before enrollment; or using NSAIDs, or other analgesic drugs, or external ointment 24 h before the baseline assessment

(5) Severe malformation because of gouty arthropathy or disability resulting from stiffness

(6) Pregnancy or lactation

(7) Allergic constitution or a history of allergy

(8) Serum creatinine (Scr) exceeding the upper limit of the reference value

(9) Liver function and AST and ALT levels 1.5 times higher than the normal upper limit

(10) Clinically significant arrhythmia

(11) History of alcohol or drug abuse

(12) Severe cerebrovascular, renal, liver, or hematopoietic comorbidities, cancer, or mental disorders;

(13) Participated in other clinical trials in the last 3 months

(14) Referring to the judgment by investigators: some other diseases or situations that might cause a lower possibility of recruitment or complicate the enrollment, such as missing visits due to frequent changes in the workplace.

2.3 Randomization and intervention

Patients with AGA were randomly divided into three groups. Following the distribution sequence, random numbers were created using SAS9.2 edition (Straits Leading Pharmaceutical R&D Co. Ltd., Heping District of Shenyang) by an independent statistician from the CMU1h Clinical Trials (GCP) center. Every random number was put into a serially numbered opaque envelope and screened by clinical coordinators. After screening, the clinical researchers provided patients with treatment according to the randomized serial number.

Every eligible patient was given a specific treatment number, which was a fixed number for the whole trial used as the basis of drug allocation. CQBG, a medicine herb preparation, was produced adhering to a good production standard by Jiangyin Tianjiang Pharmaceutical Co. Ltd., Jiangsu province. The components and quality control mapping of this powder is shown in *Supplementary file 1*. Diclofenac diethylamine emulsifier was produced by Novartis Pharma (Beijing) Stein AG.

One pack of CQBG (30 g) was dissolved in water, and the dosage of CQBG and diclofenac diethylamine emulsifier was regulated (1 cm outside the pain area; 1–2 cm in thickness for topical medicine [15], three times a day).

2.4 Ethic permission and registration

This study was performed following the standard of International Coordinating Committee on Global Partnerships and the revised edition of the Declaration of Helsinki. It was registered in ChiCTR (ChiCTR1800018020). Every participator endorsed the informed consent on a voluntary basis. Every participator endorsed the informed consent on a voluntary basis.

2.5 Observation indicators

2.5.1 Primary clinical outcome indicators

(1) Change in the VAS score in target joint: 0 for no pain and 10 for unbearable pain. The VAS score was evaluated three times a day with consistency among groups in terms of patients' feeling of pain, and its mean value was taken as the VAS score of the day.

(2) Onset-Time of pain improvement in the target joint: VAS < 3 was defined as pain improvement.

(3) Change in pain duration in the target joint: The duration of target joint pain was obtained from a daily pain recording card, and the change in pain duration was defined with a result of pain duration on the testing day minus pain duration on the previous day. To reduce deviation, the patients were stratified into groups 0–24 h, 24–48 h, and 48–72 h according to the disease course of acute gout. The change in pain duration on days 1–4, 7, 10, and 14 was observed.

(4) Swelling score: 1 for no arthrocele, 2 for palpable arthrocele, 3 for macroscopic arthrocele, and 4 for swelling exceeding the joint edge. The swelling change in all groups on days 0, 7, and 14 was observed.

2.5.2 Secondary outcome indicators

UA, CRP, and ultrasound examinations of the thickness of the inflammatory synovium of joints were evaluated once before and after the treatment.

2.6 Safety evaluation

Examinations including physical examination, blood routine, urine routine, and hepatorenal function as well as records of all adverse events were assessed and analyzed with drug dependency.

2.7 Statistical analysis

Data were analyzed with SPSS 23.0 software, while measurement data were presented with $\bar{x} \pm s$. Data meeting normal distribution comparison adopted variance analysis; otherwise, the nonparametric test was used. The VAS score was obtained using analysis of variance for repeated measurement and rank-sum test for ranked data, while enumeration data were compared using the χ^2 test. A P value < 0.05 indicated a statistically significant difference.

3. Results

3.1 General data

A total of 90 patients were recruited and distributed into control, T1, and T2 groups in a ratio of 1:1:1. Three patients from the control group and two from the T1 group failed to complete the study due to their bad compliance, while one from the T2 group could not complete the study because of pruritus. Table 1 showed the baseline characteristics of patients, and Fig. 1 showed the recruitment procedure.

Table 1
Characteristics of the participants.

variable	control group n = 27	treatment group1 n = 28	treatment group2 n = 29
Age (years, mean \pm SD)	45.00 \pm 3.17	48.00 \pm 7.05	46.00 \pm 7.49
Men, n (%)	19.00(70%)	20.00(71%)	19.00(66%)
History of gout (years, median (range))	3.00(0–9)	3.00(0–10)	3.00(0–11)
BMI (kg/m ² , mean \pm SD)	32.00 \pm 5.00	31.00 \pm 4.00	32.00 \pm 6.00
Uric acid (pre-treatment) (μ mol/L, mean \pm SD)	480.00 \pm 98.00	470.00 \pm 90.00	480.00 \pm 98.00
Onset time, n (%)			
\leq 24 h	3.00(11%)	4.00(14%)	5.00(17%)
24–48 h	9.00(33%)	8.00(28%)	8.00(28%)
48–72 h	15.00(56%)	16.00(58%)	16.00(55%)
Index joint			
Metatarsophalangeal joint 1	4.00(15%)	3.00(11%)	4.00(14%)
Other foot joints,	5.00(19%)	5.00(18%)	9.00(31%)
ankle	5.00(19%)	6.00(21%)	7.00(24%)
knee	6.00 (22%)	9.00(32%)	7.00(24%)
wrist	1.00(4%)	1.00(4%)	0
Hand	2.00(7%)	3.00(11%)	2.00(7%)
Elbow	1.00(4%)	0	0
multiple joints	3.00(10%)	1.00(4%)	0
Joint swelling			
No swelling	0	2.00(6%)	0
Palpable	6.00(22%)	8.00(29%)	8.00(28%)
Visible	6.00(22%)	8.00(29%)	10.00(34%)
Bulging beyond joint margins	15.00(56%)	10.00(36%)	11.00(38%)
Activity, n (%)			
*The baseline characteristics of the participants were similar across three groups.(<i>P</i> all \geq 0.05)			

variable	control group n = 27	treatment group1 n = 28	treatment group2 n = 29
No restricted	0	0	0
Moderate restricted	5.00(19%)	7.00(25%)	9.00(32%)
Significantly restricted	9.00(33%)	11.00(39%)	10.00(34%)
Unbearable, cannot take care of themselves	13.00(48%)	10.00(36%)	10.00(34%)
Smoke use(%)	17%	24%	22%
Drink(%0	35%	40%	38%
*The baseline characteristics of the participants were similar across three groups.(P all ≥ 0.05)			

3.2 Main outcome indicators

3.2.1 Comparison of the VAS score of the target joint on days 1, 2, 3, 4, 7, and 14 in the three groups

After treatment, VAS scores of the target joint in the three groups dropped down on days 1, 3, 5, and 7; some of them were statistically significant ($P < 0.05$). The VAS score on day 3 was significantly lower in the T2 group than in the control group ($P < 0.05$). The VAS scores on days 4 and 7 in treatment and day 14 in observation were significantly lower in the T2 group than in the T1 and control groups, as shown in Fig. 2.

3.2.2 Comparison of change in pain duration of the target joint in the three groups

A gradual decline in the pain duration of the target joint in the three groups was observed after the treatment. From day 2, the reduction in pain duration was significantly better in the T2 group than in the control group ($P < 0.05$); on day 4, the reduction in pain duration was much better in the T2 group than in the T1 group ($P < 0.05$), as shown in Table 2.

Table 2
Comparison of change in pain duration change in the target joint in the three groups

	pain duration	Group	After treatment						
			1 day	2 day	3 day	4 day	7 day	14 day	
Changes in pain duration	≤24 h	control group	1.00 ± 0.33	2.20 ± 0.55	4.50 ± 0.33	4.00 ± 0.66	1.30 ± 0.22	0.10 ± 0.22	
		treatment group1	1.10 ± 0.18	2.50 ± 0.50	4.60 ± 0.50	4.20 ± 0.50	1.40 ± 0.38	0.20 ± 0.25	
		treatment group2	1.30 ± 0.36	2.60 ± 0.32	4.80 ± 0.32	4.50 ± 0.36	1.70 ± 0.20	0.10 ± 0.32	
	comparisons <i>P</i>	c-t1		0.437	0.537	0.348	0.702	0.900	0.721
		t1-t2		0.509	0.079	0.323	≤0.05*	≤0.05*	≤0.05*
		c-t2		0.303	≤0.05*	≤0.05*	≤0.05*	≤0.05*	≤0.05*
	24–48 h	control group		1.20 ± 0.29	2.40 ± 0.43	4.00 ± 0.67	3.50 ± 0.72	2.20 ± 0.29	0.20 ± 0.26
		treatment group1		1.30 ± 0.39	2.70 ± 0.48	4.20 ± 0.48	3.60 ± 0.47	2.30 ± 0.39	0.20 ± 0.28
		treatment group2		1.50 ± 0.38	3.00 ± 0.25	4.60 ± 0.57	3.80 ± 0.31	2.50 ± 0.50	0.20 ± 0.11
comparisons <i>P</i>	c-t1		0.657	0.297	0.625	0.620	0.657	0.934	
	t1-t2		0.429	0.311	0.054	≤0.05*	≤0.05*	≤0.05*	
	c-t2		0.186	≤0.05*	≤0.05*	≤0.05*	≤0.05*	≤0.05*	
48–72 h	control group		1.70 ± 0.52	2.30 ± 0.68	3.00 ± 1.07	3.10 ± 0.48	2.50 ± 0.47	0.20 ± 0.24	
	treatment group1		1.40 ± 0.36	3.00 ± 0.75	4.60 ± 1.3	3.40 ± 0.47	2.60 ± 0.38	0.30 ± 0.23	
	treatment group2		1.60 ± 0.30	3.50 ± 0.75	3.50 ± 1.53	3.50 ± 0.85	2.90 ± 0.42	0.20 ± 0.06	
comparisons <i>P</i>	c-t1		0.130	0.063	0.052	0.346	0.742	0.393	
	t1-t2		0.191	0.150	0.925	≤0.05*	≤0.05*	≤0.05*	
	c-t2		0.566	≤0.05*	≤0.05*	≤0.05*	≤0.05*	≤0.05*	

*The difference was statistically significant.

pain duration	Group	After treatment					
		1 day	2 day	3 day	4 day	7 day	14 day
Multiple comparisons <i>P</i>		0.063	0.05*	0.05*	0.05*	0.05*	0.063

*The difference was statistically significant.

3.2.3 Onset-Time comparison of pain improvement of the target joint in the three groups

Pain improvement of the target joint in the T2 group occurred earlier than that in the control and T1 group with statistical significance in comparison ($P < 0.05$), as shown in Table 3.

Table 3
Comparison of onset-time of pain improvement of the target joint in three groups (mean \pm SD)

Group	Number of cases	Onset-time of pain improvement(d)
Control	27	7.70 \pm 4.20
T1	28	6.68 \pm 3.30
T2	29	4.17 \pm 1.18 ^{&#}

Comparison between treatment group 2 and control group [&] $P < 0.05$; Comparison between treatment group 2 and treatment group 1 [#] $P < 0.05$.

3.2.4 Comparison of the swelling score of the target joint in the three groups

The analysis of repeated measurement and comparison between pretreatment and post-treatment showed that the swelling scores on days 7 and 14 in the three groups decreased remarkably ($P < 0.05$). The swelling score on day 7 was significantly lower in the T2 group than in the control ($P < 0.01$) and T1 groups ($P < 0.05$) while the score in the T1 group was significantly lower than that in the control group ($P < 0.05$). On observation day 14, the swelling score was significantly lower in the T2 group than in the control ($P < 0.01$) and T1 groups ($P < 0.05$), and significantly lower in the T1 group than in the control group ($P < 0.01$), as shown in Fig. 3.

3.3 Comparison of change in CRP, UA, and thickness of the synovium of target joints before and after the treatment in the three groups

Compared with pretreatment, CRP and blood UA levels in the control and treatment groups decreased significantly after the treatment ($P < 0.05$), but no statistically significant difference was observed between the three groups, as shown in Tables 4 and 5. In terms of change in the thickness of the

synovium of target joints after treatment, a significant improvement was seen in the T2 group(Fig. 4) ($P < 0.05$), which was better than that in the control group (basic treatment group), as shown in Table 6.

Table 4
Comparison of the average changes of CRP in the three groups.

Group		Before treatment	Week 1	Week 2	Comparisons P
CRP(mg/L)	control group	45.00 ± 22.00	14.00 ± 4.00	7.00 ± 3.00	0th-7th: $P < 0.05^*$
					7th-14th: $P < 0.05^*$
					0th-14th: $P < 0.05^*$
	treatment group1	46.00 ± 25.00	11.00 ± 4.00	6.00 ± 3.00	0th-7th: $P < 0.05^*$
					7th-14th: $P < 0.05^*$
					0th-14th: $P < 0.05^*$
	treatment group2	47.00 ± 23.00	13.00 ± 5.00	5.00 ± 3.00	0th-7th: $P < 0.05^*$
					7th-14th: $P < 0.05^*$
					0th-14th: $P < 0.05^*$
group comparisons P		$P > 0.05$	$P > 0.05$	$P > 0.05$	
*The difference was statistically significant.					

3.4 Safety evaluation

No severe adverse event was observed in the three groups. The cumulative incidence of adverse reactions in the T1, T2, and control groups was 10.7%, 6.9%, and 7.4%, respectively, showing no statistically significant difference in three groups, as shown in Table 7.

Table 7
Adverse reactions

	control group	treatment group1	treatment group2
Total adverse effects	2/27	3/28	2/29
Gastric or abdominal pain	2(7.4%)	2(7.1%)	1(3.4%)
Edema	0	1(3.6%)	0
Skin Itch	0	0	1(3.4%)

4. Discussion

The incidence of gout continues to increase every year, and an acute attack is often triggered by multiple factors in its chronic course. NSAIDs, systemic corticosteroids, and oral colchicine are recommended by the 2012 ACR guide for treating AGA [16]; however, the side effects of these drugs limit their use in the clinic. Recent studies on AGA treatment with traditional Chinese medicine have shown unique advantages and fewer side effects[4]. In this study, the T2 group had a significant reduction in the VAS score of joint pain, arthrocele, and decreasing pain duration compared with the control and T1 group ($P < 0.05$), indicating that the external application of CQBG on AGA, combined with Western–medicine–basic treatment, had therapeutic effects of quickly alleviating clinical symptoms such as pain and swelling, shortening disease course, and reducing patients’ burden.

Accumulated dampness-heat syndrome is a common syndrome of AGA in the clinic. In the theory of traditional Chinese medicine, a deficiency of spleen qi and imbalance of metabolism of water and food can induce the accumulation of damp. Additionally, eating too much greasy food with stronger flavor can cause accumulation of damp, leading to heat accumulation in the skin and joints and resulting in a gout attack. Hence, the external application of prescription in traditional Chinese medicine for gout focused mainly on clearing heat and expelling dampness, which was demonstrated in some studies with clear efficacy for AGA, namely, good therapeutic effect in controlling symptoms in acute gout and reducing recurrence rate. For instance, oral Jiawei Simiao Powder and external application of Sihuang water–honeyed pill had significant effects in decreasing the blood UA level and improving the joint function of patients with AGA [17].

In this study, CQBG was found to be effective in improving the function of anti-inflammatory and analgesic drugs as well as lowering blood CRP and blood UA levels. Its mechanism might be related to

the decline in inflammatory cytokine release caused by effective components of this compound drug. CQBG is formulated with *Cortex Phellodendri* and *Herba tuberculata speranskia*. *Cortex Phellodendri* with cold nature was originally documented in the *Holy Husbandman's Classic on Roots and Herbs* (finished in 1616 AD), which was always used against pyogenic infections with active elements of tetrandrine and berberine that exerted anti-inflammatory and immunoregulatory effects by reducing the expression of inflammatory cytokines and increasing the expression of anti-inflammatory cytokines [18, 19]. Clinically, *Cortex Phellodendri* can be used in the treatment of arthritis, gout, and so forth, through lowering UA and creatinine levels in model rats with hyperuricemia and inhibiting arthrocele in model rats with acute gout arthritis[20]. *Herba tuberculata speranskia*, which is pungent and warm in nature, was originally documented in *Jiuhuang Beneao* (finished in 1525 AD) with the efficacy of expelling damp and swelling and relieving pain. The anti-inflammatory effect of this Chinese traditional medicinal crop and its components and the inhibition of platelet aggregation were shown in pharmacological studies. Moreover, this drug reduced swelling of the paw in model rats with arthritis; inhibited the proliferation and transfer of synovial cells and release of inflammatory cytokines; decreased the protein expression of inflammasome NLRP3, caspase-1, and IL-1 β ; inhibited inflammatory cell infiltration and angiogenesis; promoted apoptosis; reduced serum inflammatory factors IL-1 β and TNF- α levels; and significantly inhibited the inflammatory reaction. Clinically, *Herba tuberculata speranskia* is used mostly for external application in rheumatic arthralgia, bone and muscle contracture, and pyogenic infections[13, 21–25]. In summary, the external application of this compound had antibacterial, anti-inflammatory, analgesic, and anticoagulatory effects against AGA. Among these, the anti-inflammatory function helped reduce the local swelling of joints and prevent local infection. The analgesic effect relieved anxiety produced by pain, and the anti-coagulatory effect helped in the remission of local swelling and pain besides thrombogenesis prevention. Moreover, drugs were efficiently absorbed percutaneously, achieving an obvious clinical effect in a short time.

The external application of this compound combined with Western–medicine–bastic treatment with a significant therapeutic effect in lowering CRP and blood UA levels of patients with AGA was better compared with the conventional treatment (control) group ($P < 0.05$). CRP is a nonspecific indicator reflecting inflammatory activity, which is involved in the pathological process of chemotaxis and activation of inflammatory cells. CRP is a polypeptide consisting of five identical polypeptide chain subunits and also a calcium-binding protein. It is rarely found in healthy people but rises quickly during inflammation and acute injuries in the body and drops down rapidly with an improvement in condition. Therefore, CRP is important in nonspecific immunity. Additionally, it plays an important role in the clinic by reflecting whether rheumatoid fever and gout can be controlled or whether relapse occurs in patients. CRP in the inflammatory joint fluid positively correlates with CRP in blood. CRP in the inflammatory joint fluid, secreted by monocytes and lymphocytes of the synovium, has high expression in the lower lining layer of the inflammatory synovium of joints with the activation of the NF- κ B/P65 pathway of synoviocytes and suppression of its nonspecific factor I κ B. CRP can significantly increase the levels of inflammatory factors such as IL-6, MMP-3, and TNF- α produced by synoviocytes, promoting inflammation of the joints. Hence, CRP not only reflects the activity of joint inflammation but also

participates in the development of arthritis as a pro-inflammatory factor, as shown in one study [26]. Therefore, it was speculated that one of the therapeutic mechanisms of CQBG on AGA might be through reducing the CRP level, inhibiting the NF- κ B/P65 pathway, and reducing the expression of inflammatory factors.

CQBG treatment group could lower the blood UA level and reduce the accumulation of urate crystals in joints, thus further reducing inflammatory cell infiltration and improving the arthritis profile. UA exists *in vivo* as ionic UA salts, and urate crystal starts to accumulate in tissues when the serum UA level exceeds the normal threshold. A continuous accumulation of urate crystals in joints triggers an acute inflammatory reaction with severe arthralgia, swelling, burning, redness, and difficulty in the movement of involved joints. Meanwhile, early symptoms of mild joint discomfort or stabbing pain can occur in the attack and reach a peak within 24 h. Hence, one of the objectives in clinical treatment is to reduce the blood UA level by inhibition of uric acid production and promotion of the excretion of uric acid. The experimental results indicated that the extract of *Cortex phellodendri* (One of the components of CQBG) can significantly inhibit xanthine oxidase (XOD) activity in liver, down regulate XOD mRNA and protein expression, and significantly reduce the expression level of mURAT1 mRNA and protein in kidney, therefore, which might be dual effects include the inhibition of production of uric acid and the reabsorption of uric acid in the kidney in hyperuricemia mice [27].

Ultrasound has the characteristics of easy operation, noninvasiveness, flexibility, and high sensitivity and hence provides vivid and visualized monitoring and assessment for patients with gout [28]. Therefore, it is widely applied in the diagnosis and evaluation of gouty arthritis. Synovium thickening was a typical manifestation of gout in the acute stage. In this study, a significant decline in the thickness of the synovium of joints was observed in the CQBG treatment group compared with the control group. In this study, the detection rate of double track sign under ultrasound is not high. The reason may be that the patients in this study were in-patient with serious condition, and most of them were accompanied with obvious gout stone and bone destruction, so the rear serious sound attenuation affected the detection rate. At the same time, this double track sign should be differentiated from calcium pyrophosphate deposition in the joint (also known as pseudogout).

5. Conclusions

In this study, the external application of CQBG combined with Western-medicine-bastic treatment was used for treating AGA with dampness-heat syndrome, showing good and safe clinical effects in terms of quickly alleviating pain and main clinical symptoms as well as inhibiting the inflammatory reaction. Furthermore, it reduced the use of NSAIDs, alleviated patients' burden, and improved their quality of life.

Abbreviations

NSAIDs
nonsteroidal anti-inflammatory drugs;

CQBG
compound Qingbi granules;
AGA
acute gouty arthritis;
VAS
Visual Analogue Scale/Score;
BMI
body mass index;
CRP
C-reactive protein;
UA
uric acid;
IL-6
Interleukin-6;
TLR
toll-like receptor;
ASC
apoptosis-associated speck-like protein containing a CARD;
NF
nuclear factor;
GCP
Guideline for Good Clinical Practice;
MMP
matrix metalloproteinase;
XOD
xanthine oxidase;
mURAT1
mouse urate anion transporter 1;
TNF- α
tumor necrosis factor-alpha;
NLRP3
NOD-like receptor family, pyrin domain containing 3.

Declarations

Ethics approval and consent to participate

This study was performed following the standard of International Coordinating Committee on Global Partnerships and the revised edition of the Declaration of Helsinki. It was registered in ChiCTR (ChiCTR-TRC-13003200). Every participant endorsed the informed consent on a voluntary basis. Every participant endorsed the informed consent on a voluntary basis.

Consent for publication

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

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was funded by the National Natural Science Foundation of China(No.81973661).

Authors' Contributors

RS conceived the study and ZJ supervised its performance. MFY executed the study and RS and MFY wrote the manuscript. RS and LYT performed data management and statistical analysis.

Acknowledgements

Not applicable

References

1. Stamp LK, Dalbeth N. Prevention and treatment of gout. *Nat Rev Rheumatol*. 2019;15(2):68–70.
2. Liu R, Han C, Wu D, Xia X, Gu J, Guan H, Shan Z, Teng W. Prevalence of hyperuricemia and gout in Mainland China from 2000 to 2014:a systematic review and meta-analysis. *Biomed Res Int*. 2015;2015:762820.
3. Wechalekar MD, Vinik O, Moi JH, Sivera F, van Echteld IA, vanDurme C, Falzon L, BombardierC, Carmona L, Aletaha D, Landewé RB, van der Heijde DM, Buchbinder R. The efficacy and safety of treatments for acute gout: results from a series of systematic literature reviews including Cochrane reviews on intraarticular glucocorticoids, colchicine,nonsteroidal antiinflammatory drugs, and interleukin-1 inhibitors. *J Rheumatol Suppl*. 2014;92:15–25.
4. Chi X, Zhang H, Zhang S, Ma K, et al. Chinese herbal medicine for gout: a review of the clinical evidence and pharmacological mechanisms. *Chin Med*. 2020;15:17.

5. Huang JY, Zhang Y, Wu L, Li XP, Chen K. Analysis of tongue image in 216 patients with gout. *J Shandong Univ Tradit Chin Med*. 2019;43(02):159 – 62,66.
6. Wang XL, Liu N, Qin TN, Di PT, Li ZF, Peng JY. Professor Peng Jiangyun's experience in treating acute gout in dampness. *J New Chin Med*. 2018;50(05):256–7.
7. Wu HH, Liu X, Guo LZ, Ji B. Treatment of acute gout attack with integrated traditional Chinese and western medicine. *J Changchun Univ Chin Med*. 2019;35(01):73–5.
8. Wang LZ. Effect of modified simiao Powder Decoction on inflammatory cytokines and multiple target regulatory signaling pathway for rats with acute gouty arthritis. *J Sichuan Tradit Chin Med*. 2018;36(04):69–72.
9. Liu HY, Wang L. Effects of Tongfengan mixture on ankle joint swelling, MSU crystal numbers and blood C-reactive protein expression in the rats with acute gout. *World J Integr Tradit West Med*. 2018;13(11):1549–52.
10. Tian S, Miao MS. Mechanism of External Use of Traditional Chinese Medicine"Three Micro-Regulations for Balance"Based on Neural-endocrine-immune Network. *Chinese Journal of Experimental Traditional Medical Formulae*. 2019;25(04):6–12.
11. Li XK, Feng S, Zheng YC, Liu Mei, Zhang J, Ma L. Research progress on chemical constituents and bioactivity of *Phellodendri Chinensis Cortex* and *Phellodendri Amurensis Cortex*. *Drug Evaluation Research*. 2019;42(05):1033–7.
12. Xiong SG, Zhang YJ, Fu WX, Zhang XC, Li ZL, Zhong ZH, Zhu YX. Clinical observation on 263 cases of soft tissue injury treated by Touguxiang massage cream. *Journal of Guiyang University of traditional Chinese Medicine*. 1992;(04):27–29.
13. Wang X, Cui JR, Xiao ZP, Zhang YY, Li CL, Zhao YY, Cai SQ. A comparative study on the anti-inflammatory and analgesic effects of Tougucao. *Journal of Beijing Medical University*. 1998;30(2):145.
14. Vargas-Santos AB, Taylor WJ, Neogi T. Gout Classification Criteria:Update and Implications. *Curr Rheumatol Rep*. 2016;18(7):46.
15. Zhao H, Miao MS. A Review of the Method of External Treatment of Traditional Chinese Medicine[P]. 3rd International Conference on Green Materials and Environmental Engineering (GMEE 2017),2017.
16. Robert Terkeltaub
Dinesh Khanna PPKhanna, Manjit JDFitzGerald, Bae KSingh,S, Neogi T, Merrill MHPillinger,J, Lee S, Prakash S, Kaldas M, Maneesh Gogia, Fernando Perez-Ruiz, Will Taylor, Frédéric Lioté, Hyon Choi, Jasvinder A.Singh, Nicola Dalbeth, Sanford Kaplan, Vandana Niyyar, Danielle Jones, Steven A.Yarows, Blake Roessler, Gail Kerr, King C, Levy G, Furst DE, Edwards NLawrence, Mandell B, Schumacher HRalph, Robbins M, Wenger N. Robert Terkeltaub. 2012 American College of Rheumatology guidelines for management of gout. Part 2:therapy and antiinflammatory prophylaxis of acute gouty arthritis. *Arthritis Care Res (Hoboken)*. 2012;64(10):1447-61.
17. Zhou HM, Chen SQ, Sun BG, Yin LR, Ye XY, Chen ZX. A Clinical Research of Jiawei Simiaosan Oral Administration Combined With the External Application of Sihuangshuimi in the Treatment of Acute

- Gouty Arthritis. *Journal of Chinese Medicinal Materials*. 2007;Sep;30(9):1196–8.
18. Zhang LZ, He HM, Li XF, Lv JS, Huang YH. Relationship between effect of tetrandrine on pleurisy and cAMP of inflammatory neutrophils. *Chinese Pharmacological Bulletin*. 2016;12(7):791–6.
 19. Gao Y, Wang F, Song Y, Liu H. The Status of and Trends in the Pharmacology of Berberine:A Bibliometric Review[1985–2018]. *Chin Med*. 2020; Jan 20;15:7.
 20. Lin B. Comparison of the Nourishing Yin effect and anti-gout effect of unprocessed and different processed products of cortex phellodendri chinensis. *Ji₁ed Theor&Pra*. 2016;29(19):3304–5,3308.
 21. Yang F, Jin RM, Fan Bin, Zhang N, Yang LJ, He WQ, Fu SG. Experimental study on bacteriostatic and anti-inflammatory effects of Compound Tougucao Solution. *SHJTCM*. 2017;51(05):82–5.
 22. Kim HR, Kim BM, Won JY, Lee KA, Ko HM, Kang YS, Lee SH, Kim KW. Quercetin, a plant polyphenol, Has potential for the prevention of bone destruction in rheumatoid arthritis. *J Med Food*. 2019;22(2):152–61.
 23. Yang Y, Zhang X, Xu M, Wu X, Zhao F, Zhao C. Quercetin attenuates collagen-induced arthritis by restoration of Th17/Treg balance and activation of Heme Oxygenase 1-mediated anti-inflammatory effect. *Int Immunopharmacol*. 2018;54:153–62.
 24. Ji JJ, Lin Y, Huang SS, Zhang HL, Diao YP, Li K. Quercetin: a potential natural drug for adjuvant treatment of rheumatoid arthritis. *Afr J Tradit Complement Altern Med*. 2013;10(3):418–21.
 25. Li F, Yao JH, Tian YQ, Zhang FX, Sun LJ, Tao JM. Effect of sodium ferulate on the expression of VEGF and TNF- α in serum of patients with rheumatoid arthritis. *China Pharmacy*. 2007;(23):1794–1796.
 26. Liu F. The effect of MTX on CRP induced-inflammation of rheumatoid arthritis synovial fibroblasts[D]. Hefei, ANHUI MEDICAL UNIVERSITY. 2016.
 27. Lv YZ, Hu QH, Wang X, Ou YZ, Kong LD. Effects of Ermiao Pill water extracts on imbalance of urate levels and its related genes and protein levels in hyperuricemic mice. *Chinese Traditional Herbal Drugs*. 2010;41(03):418–23.
 28. Christiansen SN, Østergaard M, Terslev L. Ultrasonography in gout: utility in diagnosis and monitoring. *Clin Exp Rheumatol*. 2018;36(Suppl 114(5):61–7.

Figures

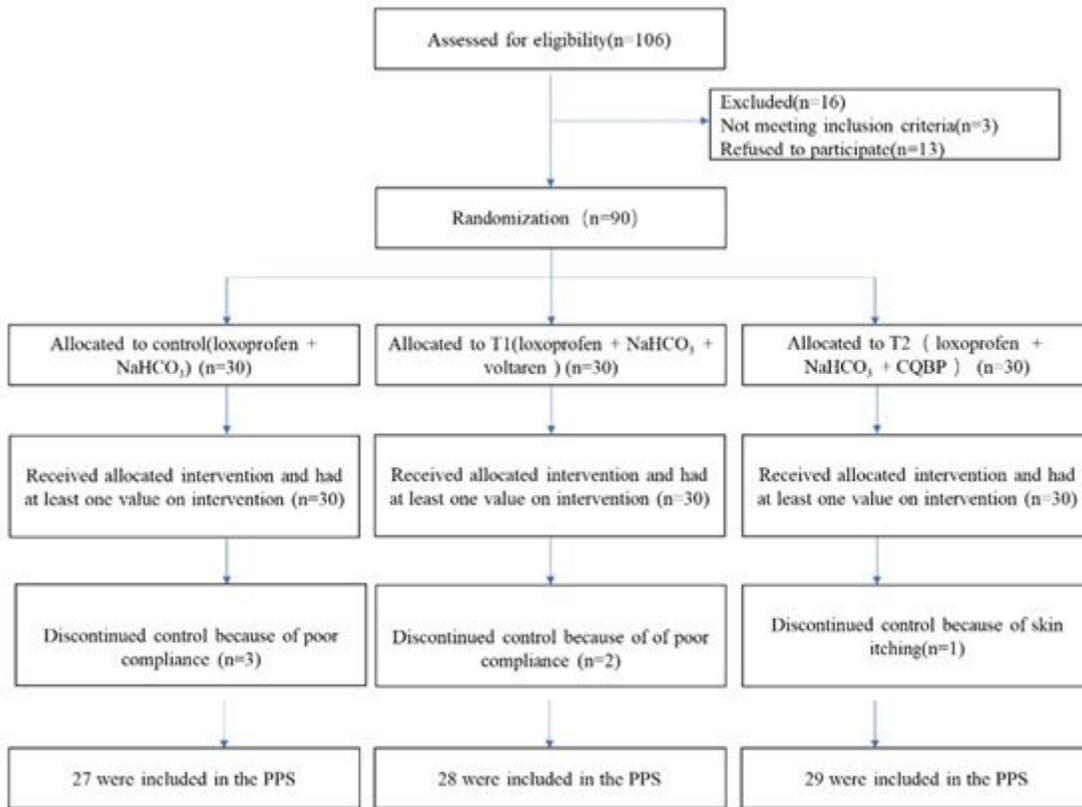


Figure 1

Patient flowchart.

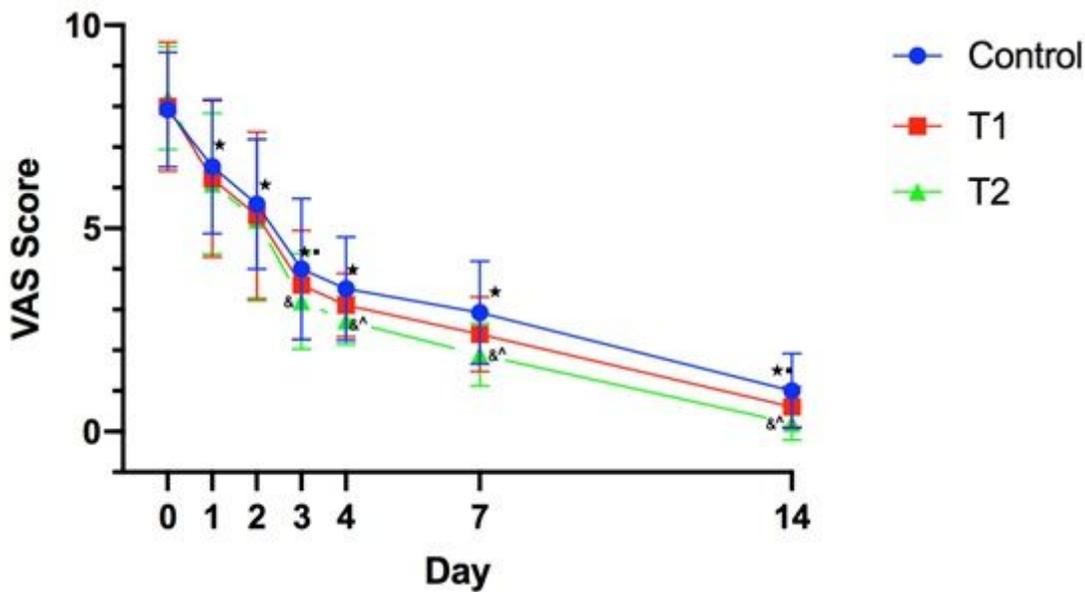


Figure 2

Comparison of the mean changes of patients VAS score in the three groups.

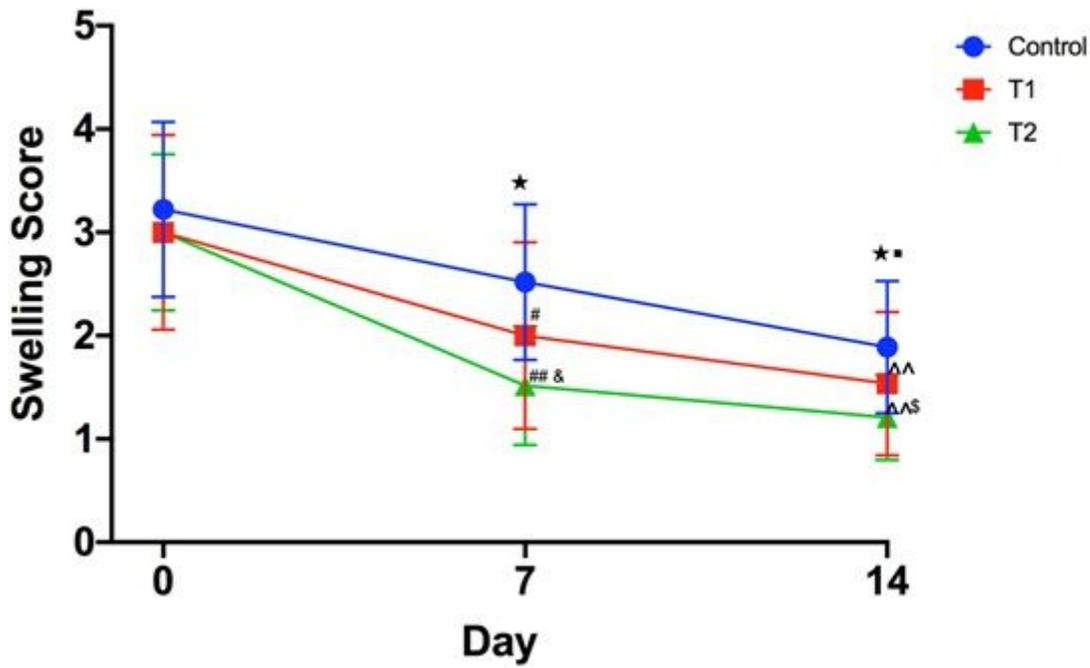


Figure 3

Comparison of swelling score in three groups on 7,14 day.

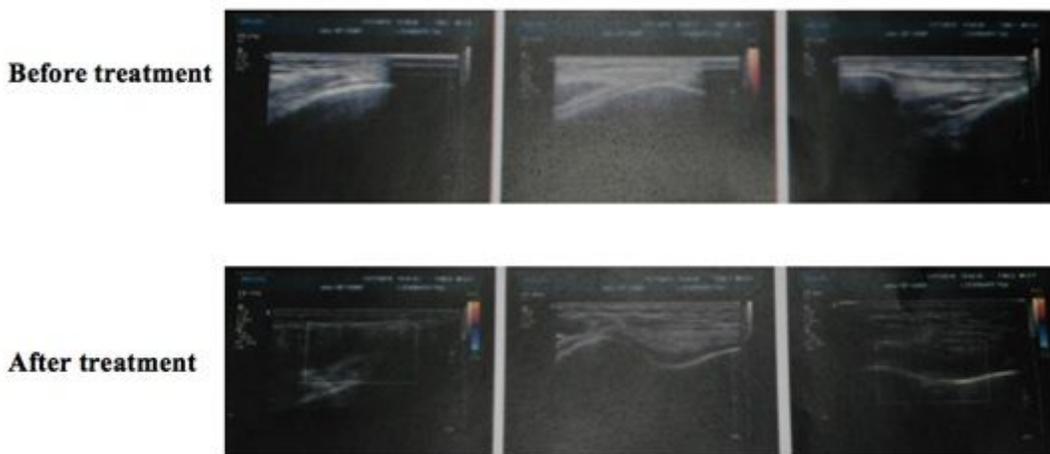


Figure 4

The measurement of synovial thickness of knee joint under color ultrasound in T2 group.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementaryfile1.docx](#)