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Original Article

Efficacy and safety of chaishituire granules in influenza treatment: a multi-center, randomized, double-blind, parallel-controlled clinical trial

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Abstract: Objectives: Information on the safety and efficacy of chaishituire granules (CSTR) for treating influenza is limited. We evaluated the safety and efficacy of CSTR in shortening the disease and fever course and improving the traditional Chinese medicine (TCM) syndrome score in influenza treatment. Methods: This multi-center, randomized, positive-drug, parallel-controlled study involved 17 hospitals across China and 221 patients with influenza aged 14-75 years. These patients met the syndrome differentiation criteria for "Wind-Heat Invading the Wei-Exterior". Patients in the CSTR group received CSTR and oseltamivir phosphate dummy capsules, whereas those in the oseltamivir control group received oseltamivir phosphate capsules and CSTR dummy granules. The primary outcomes were the time to complete remission of fever and the main clinical symptoms. The secondary outcomes were the time to elicit antipyretic effects, acetaminophen use, TCM syndrome score, remission rate of main clinical symptoms, single symptom area under the curve (AUC), and the incidence of complications or severe/critical diseases. Results: The TCM syndrome score, single symptom AUC, incidence of complications and severe/critical disease, time to complete remission of fever, main clinical symptoms, and initiation of antipyretic effects were evaluated. However, CSTR demonstrated a more rapid action and superior efficacy in alleviating sore throat compared to oseltamivir. The incidence of adverse reactions was similar between the groups. Conclusions: CSTR could be an alternative therapy for influenza virus infections.

Keywords: Chaishituire granules, influenza, fever, efficacy, oseltamivir

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Introduction

Influenza is characterized by the sudden onset of fever, headache, sore throat, nasal-respiratory discomfort, and muscle pain [1]. Influenza has a rapid onset and is generally self-limiting. However, it can lead to severe complications and even death, particularly among high-risk populations, such as older individuals, infants, pregnant women, and individuals with chronic underlying conditions or immunosuppression [2-5]. Given influenza's high transmissibility and fatality rates, effective prevention and treatment strategies are urgently needed.

Influenza treatment strategies involve symptomatic and antiviral therapies. For patients who have or are at a high risk of developing severe or progressive disease, administering neuraminidase inhibitors (NAIs), such as oral oseltamivir, inhaled zanamivir, and intravenous peramivir, is recommended [6]. Oseltamivir inhibits the release of the virus from infected cells, thereby reducing the viral replication rate. Moreover, early intervention with oseltamivir shortens symptom duration, reduces complications and hospitalization risks, and decreases the mortality rate in high-risk groups [7-19]. Nevertheless, increasing evidence suggests that influenza viruses have become resistant to NAIs [9]. Furthermore, owing to the limited availability of oseltamivir, alternative therapies are needed in certain resource-limited areas in China.

Traditional Chinese medicine (TCM) has long been used to treat infectious diseases [7]. Modern pharmacological studies have revealed that certain TCM formulae have antiviral and immunomodulatory effects [8, 12, 17]. Moreover, in clinical practice, TCM can reduce flu-like symptoms and shorten the treatment course [14, 18]. Therefore, TCM may be a promising alternative for influenza treatment. However, only a few randomized controlled trials (RCTs) have been conducted to confirm the effectiveness and safety of TCM in influenza treatment [10, 11, 19]. Therefore, conducting additional RCTs to evaluate the efficacy and safety of TCM for treating seasonal influenza is necessary.

Chaishituire granules (CSTR), a patented Chinese medicine with antipyretic effects, were formulated based on over 50 years of TCM practitioners' experience in treating acute febrile disease and exogenous fever, combined with repeated screening and validation. A pharmacological study has revealed the antipyretic, antiviral, antibacterial, anti-inflammatory, and immune-enhancing effects of CSTR [20]. Moreover, a clinical study indicated that treating Japanese encephalitis with CSTR shortens the recovery time for symptoms, such as hyperthermia, disturbed mental state, headache, vomiting, and seizures, while reducing the average hospital stay duration and improving the recovery rate [21]. When used to treat influenza, CSTR reduced the recovery time for fever and sore throat [22]; however, supporting RCT data are required. Therefore, we conducted an RCT to evaluate the efficacy and safety of CSTR in shortening the duration of disease and fever and improving the TCM syndrome score in influenza treatment.

Material and methods

Trial design

We conducted a multi-center, randomized, double-blind, parallel-controlled clinical trial (Chinese Clinical Trial Registry, https://www.chictr.org.cn/index.html, registration no.: ChiCTR1900027273; registered on 07 November 2019) between November 1, 2019, and April 1, 2020, in which the treatment group received CSTR and oseltamivir phosphate dummy capsules, while the control group received oseltamivir phosphate capsules and CSTR dummy granules.

This study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. The study protocol and informed consent form were approved by the ethics committee of each participating center (ethics approval no. of the main study center: 2019-134-K90). All participants provided written informed consent before enrollment.

Settings and participants

Patients who met all of the following criteria were included: Western medicine diagnostic criteria according to the 2019 Chinese guidelines for influenza [23]; TCM syndrome of Wind-Heat Invasion at the Wei (defensive) level; age 18-75 years; disease course within 48 h; axillary temperature ≥38°C; positive rapid influen-

za antigen test from throat swabs (colloidal gold-based immunochromatographic assay); and more than one respiratory symptom (cough, sore throat, or nasal congestion).

The TCM syndrome of "Wind-Heat Invading the Wei-Exterior" corresponds to the two primary (must include fever) and two secondary symptoms, with syndrome differentiation based on a tongue-pulse diagnosis. The primary symptoms were fever, sore throat, and slight sweating. Conversely, the secondary symptoms were headache, fatigue, cough, nasal congestion, and muscle or joint pain. Tongue-pulse manifestations included redness of the tongue body, thin or greasy tongue coating, and rapid or superficial pulse.

The exclusion criteria for patients were as follows: complicating sinusitis, otitis media, bronchitis, acute upper respiratory infection, and pneumonia; severe primary disease involving the heart, lungs, brain, liver, kidney, blood circulatory system, or endocrine system, alanine transaminase (ALT) and aspartate transaminase (AST) levels >3-fold the upper limit of the normal, and Cr level >2-fold the upper limit of the normal; immunodeficiency or immunosuppression due to AIDS, malignant tumor, organ transplantation, or immunosuppressant intake in the past 3 months use of drugs, including antibiotics, antivirals, hormones, antipyretics, and analgesics, to relieve influenza symptoms within 12 h of enrollment; influenza vaccination in the past 12 months; allergy predisposition (to two or more substances), or allergy to any components of the test drugs; women who were pregnant, planning to conceive, or breastfeeding; participation in other clinical trials in the past month; inability to cooperate owing to neurological or psychiatric disorders; and suspected or confirmed alcohol or drug abuse history.

Randomization and interventions

Participants were recruited through daily diagnoses and treatment or recruitment advertisements. The number of enrolled cases in each sub-center was fixed. Stratified block randomization was performed with the trial centers as the stratification factor. The PROC PLAN SAS procedure generated a random number table for grouping, and the participants were assigned to the CSTR experimental or oseltamivir control group at a 1:1 ratio. A double-blind, double-dummy design with two levels of blinding was used in the study. Drug blinding was performed by unblinded personnel not involved in the clinical trial; therefore, participants and researchers were unaware of treatment allocation.

The experimental group received 8 g CSTR (four times daily) and 75 mg oseltamivir phosphate dummy capsules (twice daily). In contrast, the control group received 75 mg oseltamivir phosphate capsules (twice daily) and 8 g CSTR dummy granules (four times daily). Both groups received treatment for 5 days. The patients were contacted by telephone on day 3 of the treatment. At the end of the treatment, patients followed up at the clinic.

CSTR (lot no. 191101) were provided by Sinopharm Guangdong Global Pharmaceutical Co., Ltd. (Foshan, China). Oseltamivir phosphate capsules were purchased from Roche Pharmaceuticals (Basel, Switzerland). Each drug and its placebo were similar in appearance, smell, and taste. Sinopharm Guangdong Global Pharmaceutical Co., Ltd. provided both placebo drugs.

The proportional composition of CSTR was as follows: *Chaihu* (Bupleurum root, Radix Bupleuri; 10.2%), *Huangqin* (Baical skullcap root, Radix Scutellariae Baicalensis; 10.2%), *Shigao* (gypsum, Gypsum Fibrosum; 20.4%), *Qinghao* (wormwood, Herba Artemisiae Annua; 8.2%), *Banlangen* (woad root, Radix Isatidis; 10.2%), *Jinyinhua* (honeysuckle flower, Flos Lonicerae Japonicae; 10.2%), *Dahuang* (rhubarb root and rhizome, Radix Et Rhizoma Rhei; 6.8%), *Pugongying* (dandelion, Herba Taraxaci Mongolici cum Radice; 10.2%), *Zhimu* (Anemarrhena rhizome, Rhizoma Anemarrhenae Aspheloidis; 6.8%), and *Lianqiao* (Forsythia fruit, Fructus Forsythiae Suspensa; 6.8%).

The requirements for concomitant drugs were as follows: during the observation period, no other influenza antiviral (e.g., zanamivir and peramivir) or anti-cold TCM drug was permitted; if a participant's body temperature (axillary temperature) was ≥38.5°C, 3 h after the first dose, the researcher was authorized to provide acetaminophen, as needed, to protect the participant. However, if a participant's fever persisted, other antipyretics and analgesics were

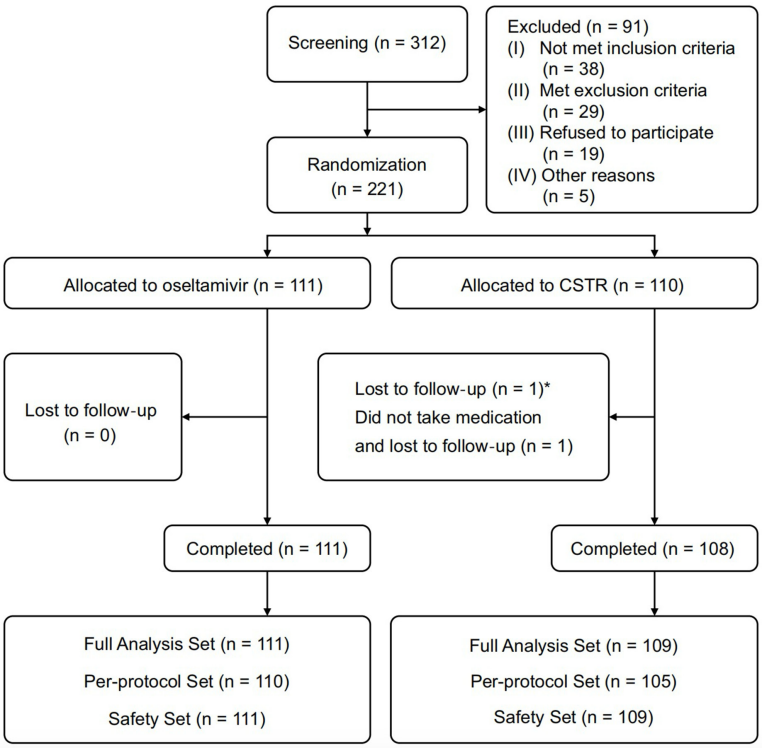

Figure 1. Flow diagram of the clinical trial design. *This patient dropped out of the trial owing to discomfort experienced after taking the drug; nonetheless, some data generated were available for full and safety analyses.

provided as necessary and recorded in the patient's medical records.

Outcomes

The primary outcome included time to remission of fever and main clinical symptoms. The time to fever remission was defined as the period required for the axillary temperature to decrease to and remain at ≤37.2°C for >24 h after treatment. The time to remission of the main clinical symptoms was defined as the interval between drug administration and a decrease in the main symptom score to 1 point (fever must be 0 points), maintained for 24 h. The scores for the main symptoms (fever, sore throat, and cough) were as follows: none, 0 point; mild, 1 point; moderate, 2 points; and severe, 3 points.

The secondary outcomes included time to the onset of antipyretic effects (time required for the body temperature to decrease by 0.5°C within 3 h of starting the medication), acetaminophen use, TCM syndrome score, time to remission of other key clinical symptoms (headache, fatigue, cough, nasal congestion, chills, and muscle or joint pain), the area under the curve (AUC, of daily symptom score and time) of individual symptoms (fever, sore throat, and cough), and incidence of influenza complications or severe/critical influenza. Influenza complications were sinusitis, otitis media, bronchitis, pneumonia, and hospitalization.

The total pre- and post-treatment TCM syndrome scores were calculated according to the classification criteria for the TCM syndrome scores (Table S1). Total syndrome score = primary + secondary syndrome scores.

Percentage decrease in the total syndrome scores = [(pre-treatment - post-treatment total scores)/pre-treatment total score] × 100.

Effectiveness evaluation criteria for TCM syndrome score: clinically cured, reduction rate of syndrome score ≥95%; markedly effective, reduction rate of syndrome score ≥70%; effective, reduction rate of syndrome score between 30% and 70%; not effective, reduction rate of syndrome score <30%. Total effective rate (%): percentage of cured, markedly effective, and effective cases of the total number of cases.

Safety evaluation

Vital sign examination, routine blood and urine tests, liver and kidney function evaluation, and electrocardiography were performed at baseline and post-treatment. Patients were continuously monitored for adverse events post-treatment; these events were recorded in the adverse event record sheet and later assessed for a causal relationship with the trial drugs.

Sample size

Based on the main outcome measurement (time to clinical symptom remission), we hypothesized that patients receiving CSTR and oselta-

Table 1. Participant demographics and baseline characteristics

Characteristic	Total	Oseltamivir	CSTR	*p-value*
Number of patients	220	111	109	0.4977
Age				
Mean (SD), y	35.1 (14.6)	34.8 (13.7)	35.5 (15.5)	0.9569
Sex				
Female, n (%)	137 (62.27)	69 (62.16)	68 (62.39)	0.9728
BMI				
Mean (SD), kg/m^2	22.01 (2.65)	22.04 (2.74)	21.98 (2.58)	0.8762
Ethnicity				
Han, n (%)	213 (96.82)	107 (96.40)	106 (97.25)	1.0000
Disease duration				
Mean (SD), h	19.80 (10.94)	20.34 (11.60)	19.24 (10.25)	0.6999
Pre-consultation medication				
None, n (%)	202 (91.82)	101 (91.82)	101 (96.19)	0.1788
Axillary temperature				
Mean (SD), °C	38.56 (0.44)	38.53 (0.38)	38.59 (0.49)	0.3877
Type of influenza virus				0.1471
Influenza A, n (%)	200 (90.91)	104 (93.69)	96 (88.07)	
Influenza B, n (%)	20 (9.09)	7 (6.31)	13 (11.93)	
Total TCM syndrome score				
Mean (SD)	14.85 (3.57)	14.70 (3.50)	15.01 (3.65)	0.5722

BMI, body mass index; CSTR, chaishituire granules; SD, standard deviation; TCM, traditional Chinese medicine.

mivir phosphate would achieve remission within 5 days with comparable efficacy. At a 0.05 significance level, with 80% power, 1.4 standard deviations, and 0.5-day non-inferiority margin, we estimated that each group would require 97 cases. Considering an anticipated dropout rate of approximately 20%, we planned to recruit 120 cases for each of the experimental and control groups, requiring 240 cases in total.

Statistical methods

Efficacy evaluation was performed using the full analysis set (FAS) and per-protocol set (PPS) datasets. In contrast, safety evaluation was performed using the safety set (SS) dataset.

Survival data are statistically described as the median, upper quartile, and lower quartile of the survival time and visualized in survival curves. Between-group comparisons were performed using the log-rank test. Descriptive statistics of quantitative data are presented as the number of cases, mean, standard deviation, minimum, median, maximum, upper quartile, and lower quartile. Between-group comparisons were performed using a grouped *t*-test or Wilcoxon signed-rank test. Descriptive statistics of qualitative data are presented as the number of cases in each category and their percentages. Additionally, between-group comparisons of categorical data were performed using the χ^2 test or Fisher's exact test. Between-group comparisons of ordinal data were performed using the Wilcoxon signed-rank test. All statistical calculations were performed using SAS v. 9.4 statistical analysis software (SAS Institute Inc., Cary, NY, USA). Unless otherwise specified, the significance level was set at $\alpha = 0.05$.

Results

Participant flow

Three hundred and twelve patients with flu-like symptoms from 17 centers were screened. Among the 221 enrolled participants, 110 were allocated to the experimental group; one was lost to follow-up, one did not take the medication and was lost to follow-up (dropout rate, 1.82%), five were not included in the PPS (4.55%), and one was not included in the FAS

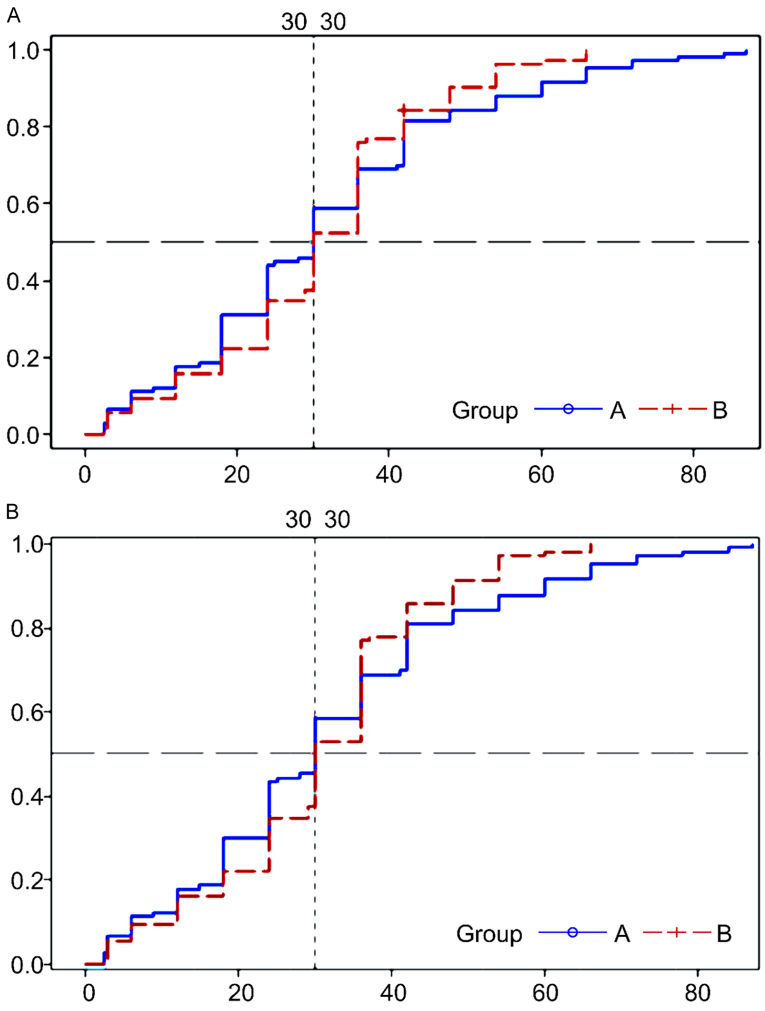

Figure 2. Survival curves for time to complete fever remission (h). A. Full analysis set survival curves. B. Per-protocol set survival curves. Groups A and B correspond to the oseltamivir and chaishituire granule treatment groups, respectively.

and SS datasets (0.91%). After excluding one patient who dropped out, the control group comprised 110 (0.9%) patients; all cases were included in the FAS and SS datasets. No statistically significant differences in dropout or rejection rates were noted between the groups. The number of cases included in the FAS for both groups was higher than the minimum required sample size according to statistical calculations (**Figure 1**).

Baseline data

The demographics and baseline characteristics of the participants included in the FAS are presented in **Table 1**. The groups had no significant differences in baseline demographics, disease duration, pre-consultation medication, axillary temperature, influenza virus type, or TCM syndrome score. Regarding the PPS, the groups had no significant differences in the baseline indicators.

Primary outcomes

Primary outcome measurements of efficacy: The FAS survival analysis indicated that the time to complete fever remission was similar in both groups: 30 (18.00, 42.00) h and 30 (24.00, 36.00) h for the oseltamivir and CSTR groups, respectively (P = 0.4776; **Figure 2A**). Furthermore, according to the PPS survival analysis, the time to complete fever remission was similar: 30 (18.00, 42.00) h and 30 (24.00, 36.00) h for the oseltamivir and CSTR groups, respectively (P = 0.3119; **Figure 2B**).

The survival analysis also revealed that, in the FAS, the time to the remission of main clinical symptoms (fever, cough, and sore throat) was not significantly different between the control, 48 (30.00, 78.00) h, and the experimental groups, 42 (36.00, 66.00) h (P = 0.2066; 95% confidence interval (CI) [-3.6895, 8.2216]; **Figure 3A**). As the lower limit of CI was greater than -12, the CSTR treatment was not inferior to that using oseltamivir. Additionally, the time to symptom remission with CSTR was shorter than that with oseltamivir (**Table 2**). Furthermore, the time to main clinical symptom remission was similar between the control, 48 (30.00, 78.00) h, and experimental groups, 42 (36.00, 66.00) h, according to the PPS analysis (P = 0.2164; **Figure 3B**).

Secondary outcome measurements of efficacy: Regarding the FAS and PPS, no significant differences were observed between the groups in the time to elicit antipyretic effects,

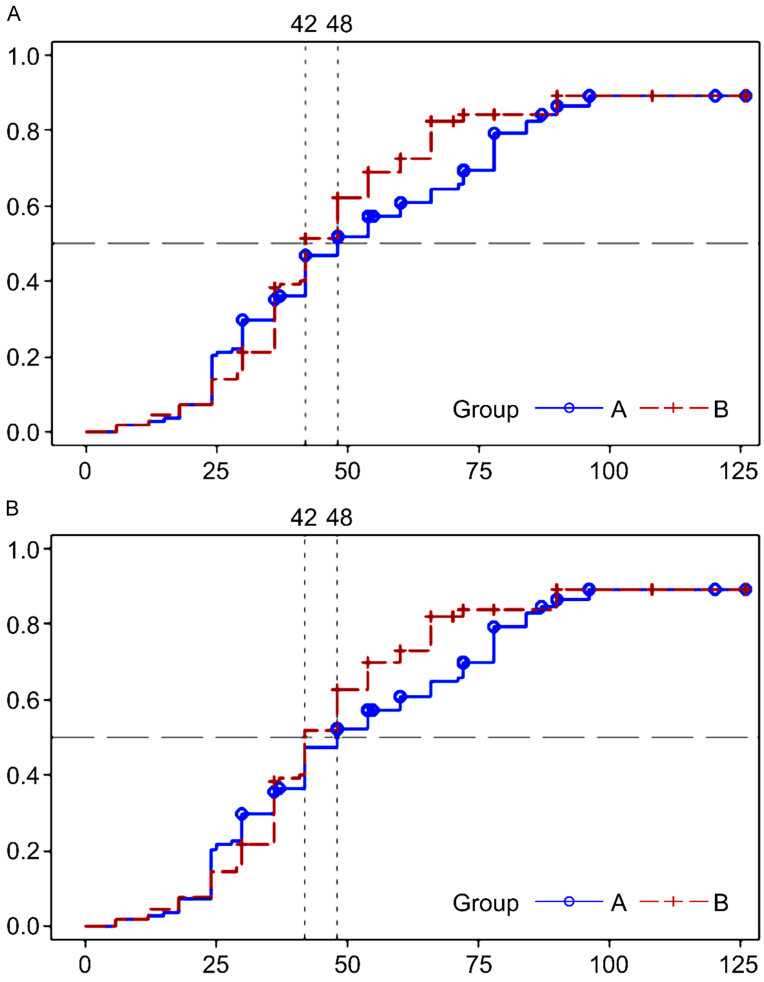

Figure 3. Survival curves for time to remission of main clinical symptoms (h). A. Full analysis set survival curves. B. Per-protocol set survival curves. Groups A and B correspond to the oseltamivir and chaishituire granule treatment groups, respectively.

percentage and total dose of acetaminophen used, therapeutic efficacy for TCM syndrome score, single symptom (fever, cough, and sore throat) AUC, and the incidence of complications or severe/critical influenza. In the PPS, the 3-day fever remission rate was higher in the CSTR group than in the oseltamivir group (100% vs. 94.55%, respectively, P = 0.0441); however, no difference was observed in the FAS. According to the FAS, the 3-day and 5-day sore throat remission rates were higher in the CSTR group (80.58% and 89.32%, respectively) than in the oseltamivir group (66.36% and 77.57%, respectively) (P = 0.0198 for 3-day and P = 0.02245 for 5-day remission rates). According to the PPS, the 3-day and 5-day sore throat remission rates were higher in the CSTR group (81.82% and 89.90%, respectively) than in the oseltamivir group (66.04% and 77.36%, respectively) (P = 0.0104 for 3-day and P = 0.0159 for 5-day remission rates) (**Table 3**).

Safety

In total, 27 participants experienced adverse events a total of 33 times during the trial. Among these, 14 participants in the oseltamivir group had adverse events 19 times, and 13 in the CSTR group experienced adverse events 14 times. No significant difference in the incidence of adverse events was observed between the two groups (P = 0.8567). Five participants experienced adverse reactions seven times. Three participants in the oseltamivir group experienced a reduction in total white blood cell (WBC) count, two of whom presented with reduced total neutrophil count (incidence, 2.7%). Moreover, two participants in the CSTR group experienced reduced WBC count (incidence, 1.83%). No significant difference existed in the incidence of adverse reactions between the groups (P = 1.0000). All the adverse reactions were mild and finally relieved or disappeared. None of the participants experienced adverse events that were too severe or led to withdrawal from the study.

Discussion

To our knowledge, this is the first clinical trial to demonstrate the effectiveness and safety of CSTR in influenza treatment. It is also a head-to-head trial of CSTR and oseltamivir application. CSTR are a patented Chinese medicine; therefore, we combined Western medicine and TCM evaluation systems to assess its effectiveness and safety and innovatively set time to complete remission of fever and main clinical symptoms as the primary outcomes. CSTR efficacy was comparable to that of oseltamivir regarding time to remission of

Table 2. Non-inferiority test for time to remission of the main clinical symptoms

Observed outcome Time to remission of main clinical symptoms	FAS			PPS		
	Difference	Lower limit of 95% CI	Upper limit of 95% CI	Difference	Lower limit of 95% CI	Upper limit of 95% CI
Oseltamivir-CSTR, h	-2.2661	-8.2216	3.6895	-2.4914	-8.4672	3.4844
CSTR-Oseltamivir, h	2.2661	-3.6895	8.2216	2.4914	-3.4844	8.4672

CI, confidence interval; CSTR, chaishituire granules; non-inferiority margin δ = -12; FAS, full analysis set; PPS, per-protocol set.

fever and other symptoms, time to elicit antipyretic effects, extent of fever control (acetaminophen use), therapeutic efficacy for TCM syndrome, single symptom AUC, and incidence of complications and severe/critical diseases. Moreover, CSTR were more rapid and effective than oseltamivir in alleviating sore throat. CSTR had a good safety profile, a low incidence of adverse reactions, and no severe adverse events.

Chaihu performs anti-oxidative, anti-apoptotic, anti-inflammatory, antiviral, antipyretic, and liver- and kidney-protective functions. Its main active ingredients - saponins and flavonoids - exert antipyretic effects by positively regulating the body temperature via prostaglandin E2 and cyclic adenosine phosphate and inhibiting the synthesis and release of endogenous pyrogens, such as tumor necrosis factors and β-endorphin. These ingredients also demonstrate antiviral effects by inhibiting HBsAg, HBeAg, and HBV-DNA production during hepatitis B viral infection [24]. *Jinyinhua* and *Lianqiao* regulate the immune pathway related to influenza A (H1N1) viral infection. *Jinyinhua* primarily modulates matrix metalloproteinase 3 activity, thereby increasing lymphocyte transformation and macrophage phagocytosis rates, whereas *Lianqiao* regulates protein kinase C-α activity [25]. These ingredients synergistically modulate the IL-2 and IL-8 signaling pathways [25]. Therefore, the anti-inflammatory, antiviral, immunomodulatory, and antipyretic effects of CSTR may be crucial in their therapeutic efficacy against influenza viral infection [22].

The time to complete fever remission using oseltamivir phosphate capsules was reportedly 20-39 h [19, 26]. Similarly, here, the time to fever remission using oseltamivir phosphate capsules was 30 h, confirming its effectiveness. The time to complete fever remission using CSTR and oseltamivir did not differ significantly, indicating that the therapeutic efficacy of both drugs was comparable. Another primary outcome was the time to remission of the main clinical symptoms. Here, patients receiving CSTR required a shorter time (42 h) than those receiving oseltamivir. Non-inferiority testing supported the result.

Participants were prohibited from taking other influenza antivirals or patented Chinese medicine for a cold to exclude the effects of other concomitant drugs. However, acetaminophen was administered when their body temperature was ≥38.5°C. In FAS and PPS, no significant differences in the percentage of use or total doses of acetaminophen were observed between the groups, suggesting that CSTR and oseltamivir phosphate capsules have similar efficacy in fever control. However, in the PPS, the 3-day fever remission rate in the CSTR group was 100%, superior to that of the oseltamivir group (94.55%). This indicates that the antipyretic effects of CSTR were more rapid than those of oseltamivir. Furthermore, the 3-day and 5-day sore throat remission rates of the CSTR group were higher than those of the oseltamivir group (14.22% and 11.75%, respectively), demonstrating that CSTR had a superior therapeutic efficacy in relieving sore throat. This may be because oseltamivir is an NAI primarily serving as an antiviral agent. Conversely, CSTR show antiviral effects alongside immunomodulatory, anti-inflammatory, and antipyretic effects. Therefore, the latter exerts beneficial effects against influenza-induced fever and local inflammation, with a specific advantage over oseltamivir phosphate capsules in treating localized sore throats.

CSTR comprise 10 Chinese medicinal ingredients, none of which have toxic components. Their percentages in the crude drug content are within a safe range. CSTR have been widely used in TCM clinical practice for over 20 years. Here, only two participants in the CSTR group

Table 3. Comparison of secondary outcome measurements

Secondary outcome measurement	FAS		*p-value*	PPS		*p-value*
	Oseltamivir (n = 111)	CSTR (n = 109)		Oseltamivir (n = 110)	CSTR (n = 105)	
Time to onset of antipyretic effects	2.50 (1.50, 3.00)	2.00 (2.00)*	0.0800	2.50 (1.50, 3.00)	2.00 (2.00)*	0.1443
Med (Q1, Q3), h						
Use of acetaminophen, n (%)	52 (46.85)	40 (36.70)	0.1270	51 (46.36)	39 (37.14)	0.1707
Total dose of acetaminophen use						
Mean (SD), g	0.73 (0.65)	0.79 (0.58)	0.3504	0.71 (0.63)	0.79 (0.58)	0.2218
Therapeutic efficacy for TCM syndrome			0.5320			0.6993
n (missing)	110 (0)	108 (1)		110 (0)	105 (0)	
Cured, n (%)	67 (60.36)	69 (63.89)		67 (60.91)	66 (62.86)	
Markedly effective, n (%)	41 (36.94)	38 (35.19)		40 (36.36)	38 (36.19)	
Effective, n (%)	3 (2.70)	1 (0.93)		3 (2.73)	1 (0.95)	
Total effective rate, n (%)	111 (100)	108 (100)	-	110 (100)	105 (100)	-
Single symptom AUC						
Fever, Med (Q1, Q3)	45.50 (27.00, 79.50)	56.50 (32.50, 79.50)	0.5120	45.75 (27.00, 79.50)	54.50 (31.50, 72.00)	0.6873
Cough, Med (Q1, Q3)	45.00 (18.00, 84.00)	48.00 (22.00, 77.00)	0.8049	45.00 (18.00, 84.00)	48.00 (21.00, 75.00)	0.8100
Sore throat, Med (Q1, Q3)	48.00 (24.00, 78.00)	45.00 (27.00, 78.00)	0.5283	48.00 (24.00, 78.00)	45.00 (27.00, 80.00)	0.5572
Incidence of complications and severe/critical influenza			0.3206			-
Occurred, n (%)	1 (0.9)	0 (0)		0 (0)	0 (0)	
Not occurred, n (%)	110 (99.1)	109 (100)		110 (0)	105 (100)	
Remission rate of main symptoms, n (%)						
3-day fever	105 (94.59)	108 (99.08)	0.1305	104 (94.55)	105 (100)	0.0441
5-day fever	111 (100)	109 (100)	-	110 (100)	105 (100)	-
3-day cough	54 (56.25)	62 (66.67)	0.1414	54 (56.84)	60 (67.42)	0.1399
5-day cough	71 (73.96)	69 (74.19)	0.9706	71 (74.74)	66 (74.16)	0.9282
3-day sore throat	71 (66.36)	83 (80.58)	0.0198	70 (66.04)	81 (81.82)	0.0104
5-day sore throat	83 (77.57)	92 (89.32)	0.0224	82 (77.36)	89 (89.90)	0.0159

AUC, area under the curve; CSTR, chaishituire granules; FAS, full analysis set; PPS, per-protocol set; Q1, lower quartile; Q3, upper quartile; SD, standard deviation; TCM, traditional Chinese medicine. *Indicates Q3 is missing.

experienced a reduced total WBC count, which was not significantly different from that in the oseltamivir group. Importantly, no severe adverse events that led to withdrawal from the study were reported, indicating that CSTR were safe for influenza treatment.

Here, we combined Western medicine and TCM evaluation systems to assess the effectiveness and safety of a patented Chinese medicine in influenza treatment. However, this study has limitations. First, throat swabs were tested only during the screening period, and follow-up tests were not performed to detect the changes in influenza antigen expression in the throat swabs during and after treatment. Therefore, evaluating the clearance effect of CSTR on the influenza virus was impossible. Second, based on the TCM theory of CSTR, the included participants were required to meet the syndrome differentiation criteria for the TCM syndrome of "Wind-Heat Invading the Wei-Exterior". However, we did not examine whether CSTR and oseltamivir were effective for patients with influenza who did not meet the TCM criteria. Finally, the classification criteria for TCM syndrome scores and the criteria for the therapeutic efficacy against TCM syndrome were quantified based on modern medicinal practices (Table S1). Using such qualitative criteria remains controversial, as it is inaccurate for quantifying TCM symptoms.

Conclusions

This study demonstrated the similar therapeutic efficacy of CSTR and oseltamivir regarding remission of fever and main clinical symptoms, time to elicit antipyretic effects, degree of fever control, therapeutic efficacy for TCM syndrome, single symptom AUC, and incidence of complications and severe/critical diseases. CSTR were more effective than oseltamivir in relieving pharyngalgia and reducing the fever remission rate. Additionally, using CSTR was safe; therefore, it could be an alternative therapy for influenza. However, further evidence-based medicine is required to demonstrate the effectiveness and safety of CSTR in influenza treatment.

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Disclosure of conflict of interest

None.

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References

[1] Lam PP, Coleman BL, Green K, Powis J, Richardson D, Katz K, Borgundvaag B, Smith-Gorvie T, Kwong JC, Bondy SJ and McGeer A. Predictors of influenza among older adults in the emergency department. BMC Infect Dis 2016; 16: 615.

[2] Centers for Disease Control and Prevention (CDC). Estimates of deaths associated with seasonal influenza - United States, 1976-2007. MMWR Morb Mortal Wkly Rep 2010; 59: 1057-1062.

[3] Cromer D, van Hoek AJ, Jit M, Edmunds WJ, Fleming D and Miller E. The burden of influenza in England by age and clinical risk group: a statistical analysis to inform vaccine policy. J Infect 2014; 68: 363-371.

[4] Siston AM, Rasmussen SA, Honein MA, Fry AM, Seib K, Callaghan WM, Louie J, Doyle TJ, Crockett M, Lynfield R, Moore Z, Wiedeman C, Anand M, Tabony L, Nielsen CF, Waller K, Page S, Thompson JM, Avery C, Springs CB, Jones T, Williams JL, Newsome K, Finelli L and Jamieson DJ; Pandemic H1N1 Influenza in Pregnancy Working Group. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. JAMA 2010; 303: 1517-1525.

[5] Thompson WW, Moore MR, Weintraub E, Cheng PY, Jin X, Bridges CB, Bresee JS and Shay DK. Estimating influenza-associated

deaths in the United States. Am J Public Health 2009; 99 Suppl 2: S225-30.
[6] Uyeki TM, Bernstein HH, Bradley JS, Englund JA, File TM, Fry AM, Gravenstein S, Hayden FG, Harper SA, Hirshon JM, Ison MG, Johnston BL, Knight SL, McGeer A, Riley LE, Wolfe CR, Alexander PE and Pavia AT. Clinical practice guidelines by the infectious diseases society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenzaa. Clin Infect Dis 2019; 68: 895-902.
[7] Chan K. Chinese medicinal materials and their interface with Western medical concepts. J Ethnopharmacol 2005; 96: 1-18.
[8] Chen N and Ren L. Modern pharmacological research and clinical application of maxingshigan decoction. Acad J Guangdong Coll Pharm 2004; 20: 545-546.
[9] Correia V, Santos LA, Gíria M, Almeida-Santos MM and Rebelo-de-Andrade H. Influenza A(H1N1)pdm09 resistance and cross-decreased susceptibility to oseltamivir and zanamivir antiviral drugs. J Med Virol 2015; 87: 45-56.
[10] Duan ZP, Jia ZH, Zhang J, Liu S, Chen Y, Liang LC, Zhang CQ, Zhang Z, Sun Y, Zhang SQ, Wang YY and Wu YL. Natural herbal medicine Lianhuaqingwen capsule anti-influenza A (H1N1) trial: a randomized, double blind, positive controlled clinical trial. Chin Med J (Engl) 2011; 124: 2925-2933.
[11] He J, Li Z, Huang W, Guan W, Ma H, Yang ZF and Wang X. Efficacy and safety of Chou-Ling-Dan granules in the treatment of seasonal influenza via combining Western and traditional Chinese medicine: protocol for a multicentre, randomised controlled clinical trial. BMJ Open 2019; 9: e024800.
[12] Huang JM, Chen DP and Yang LP. The immunomodulating effects of maxingshigan on asthma mice models. J Fujian Trad China Med 2003; 34: 38-39.
[13] Jefferson T, Jones MA, Doshi P, Del Mar CB, Hama R, Thompson MJ, Spencer EA, Onakpoya I, Mahtani KR, Nunan D, Howick J and Heneghan CJ. Neuraminidase inhibitors for preventing and treating influenza in adults and children. Cochrane Database Syst Rev 2014; 12: CD008965.
[14] Liu YL. Chinese medicine has a bright future in the prevention and treatment of influenza A. Mod Chin Med 2009; 11: 3-10.
[15] Muthuri SG, Myles PR, Venkatesan S, Leonardi-Bee J and Nguyen-Van-Tam JS. Impact of neuraminidase inhibitor treatment on outcomes of public health importance during the 2009-2010 influenza A(H1N1) pandemic: a systematic review and meta-analysis in hospitalized patients. J Infect Dis 2013; 207: 553-563.
[16] Muthuri SG, Venkatesan S, Myles PR, Leonardi-Bee J, Al Khuwaitir TS, Al Mamun A, Anovadiya AP, Azziz-Baumgartner E, Báez C, Bassetti M, Beovic B, Bertisch B, Bonmarin I, Booy R, Borja-Aburto VH, Burgmann H, Cao B, Carratala J, Denholm JT, Dominguez SR, Duarte PA, Dubnov-Raz G, Echavarria M, Fanella S, Gao Z, Gérardin P, Giannella M, Gubbels S, Herberg J, Iglesias AL, Hoger PH, Hu X, Islam QT, Jiménez MF, Kandeel A, Keijzers G, Khalili H, Knight M, Kudo K, Kusznierz G, Kuzman I, Kwan AM, Amine IL, Langenegger E, Lankarani KB, Leo YS, Linko R, Liu P, Madanat F, Mayo-Montero E, McGeer A, Memish Z, Metan G, Mickiene A, Mikić D, Mohn KG, Moradi A, Nymadawa P, Oliva ME, Ozkan M, Parekh D, Paul M, Polack FP, Rath BA, Rodríguez AH, Sarrouf EB, Seale AC, Sertogullarindan B, Siqueira MM, Skręt-Magierło J, Stephan F, Talarek E, Tang JW, To KK, Torres A, Törün SH, Tran D, Uyeki TM, Van Zwol A, Vaudry W, Vidmar T, Yokota RT and Zarogoulidis P; PRIDE Consortium Investigators, Nguyen-Van-Tam JS. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. Lancet Respir Med 2014; 2: 395-404.
[17] Raskin I, Ribnicky DM, Komarnytsky S, Ilic N, Poulev A, Borisjuk N, Brinker A, Moreno DA, Ripoll C, Yakoby N, O'Neal JM, Cornwell T, Pastor I and Fridlender B. Plants and human health in the twenty-first century. Trends Biotechnol 2002; 20: 522-531.
[18] Wang YG, Wang XJ, Du HB, Zhang W, Wang RB, Li XW and Mao Y. A report of six confirmed flu A H1N1 cases treated by Chinese and western medicine. Beijing J Trad Chin Med 2009; 28: 403-406.
[19] Wang C, Cao B, Liu QQ, Zou ZQ, Liang ZA, Gu L, Dong JP, Liang LR, Li XW, Hu K, He XS, Sun YH, An Y, Yang T, Cao ZX, Guo YM, Wen XM, Wang YG, Liu YL and Jiang LD. Oseltamivir compared with the Chinese traditional therapy maxingshigan-yinqiaosan in the treatment of H1N1 influenza: a randomized trial. Ann Intern Med 2011; 155: 217-225.
[20] Dong MJ and Tu JW. Antipyretic, antibacterial, and antiviral effects of rebining granules. J Emerg J Trad Chin Med 1996; 5: 31-35.
[21] Liu ZY, Meng Y, Chang XH, Guo J, Qiao ML and Zhao LN. Effect of chaishituire granules on the Japanese encephalitis virus CQ11-66. Chin J Med Guide 2017; 16: 78-81.
[22] Hu SY. Clinical study on chaishi antipyretic particles in the treatment of influenza. Chin Community Doctors 2018; 34: 100-101.

[23] National Health Commission of the People's Republic of China. Protocol for diagnosis and treatment of influenza (2018 revised version). Chin J Clin Infect Dis 2019; 12: 1-5.
[24] Zhang CL, Lan LL, Ren XH and Liu D. Basic research and analysis of the Chaihu and Huangqin drug pair. World Sci Technol Mod Trad Chin Med 2019; 1: 33-37.
[25] Li L, Du YW, Kou S, Zhao J, Lv C, Jiang M and Lv AP. Bioinformatics analysis on the effects of Jinyinhua and Lianqiao on the immunomodulatory pathways for influenza A H1N1. Chin J Exp Trad Med Formulae 2017; 10: 201-204.
[26] Zhang M. Effects of oseltamivir phosphate on the treatment of influenza. Contemp Symp 2020; 1: 174-175.

Table S1. Classification criteria for TCM syndrome score [2019 Chinese guidelines for influenza (National Health Commission of the People's Republic of China, 2019)]

Primary symptom	0 point	2 points	4 points	6 points
Fever (maximum axillary temperature 24 h before consultation)	≤37.2°C	37.3°C-37.9°C	38°C-39°C	>39°C
Sore throat	No	Mild pharyngeal hyperemia, absent or mild pain	Pharyngeal hyperemia and edema, obvious pain when swallowing	Pharyngeal hyperemia and edema, severe sore throat, and difficulty swallowing
Slight sweating	No	Yes	-	-
Secondary symptom	0 point	2 points	4 points	6 points
Headache	No	Mild and intermittent headache	Moderate and continuous headache	Severe headache, unable to work
Nasal congestion	No	Mild nasal congestion does not affect breathing	Nasal congestion with stridor	Severe nasal congestion with mouth breathing
Fatigue	No	Fatigue and poor vigor, but can continue daily activities and work	Mental fatigue, general weakness, barely able to continue daily activities	Severe mental and physical fatigue, difficulty in continuing daily activities
Cough	No	Occasional coughing	Intermittent coughing	Frequent coughing
Muscle or joint pain	No	Mild pain	Pain	Severe pain, difficulty in flexion and extension