



Efficacy and safety of Qinxiang Qingjie oral solution for the treatment of influenza in children: a randomized, double-blind, multicenter clinical trial

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Background: Qinxiang Qingjie (QXQJ), an oral solution containing various Chinese herbs, is indicated for pediatric upper respiratory tract infections. The treatment of influenza also shows potential advantages in shortening the duration of illness and improving symptoms. However, there is still a lack of high-quality clinical evidence to support this. The trial was to explore the efficacy and safety of QXQJ for treating pediatric influenza and provide an evidence-based basis for expanding its applicability.

Methods: A randomized, double-blind, double-dummy, positive-controlled, multicenter clinical trial was conducted in 14 hospitals in China. Children aged 1–13 years with influenza and “exterior and interior heat syndromes” as defined by traditional Chinese medicine (TCM) were randomly assigned to two groups with 1:1 ratio. Children in the test group received QXQJ oral solution and oseltamivir simulant, while the control

group received oseltamivir phosphate granules and QXQJ simulant. The duration of treatment was five days, followed by a two-day follow-up period. The primary endpoint was the clinical recovery time. Secondary endpoints included the time to defervescence, incidences of complications and severe or critical influenza, negative conversion rate, improvement of TCM syndromes, and safety profiles of the therapeutics, which mainly contained the adverse clinical events and adverse drug reactions.

Results: A total of 231 children were randomized to either the QXQJ (n=117) or oseltamivir (n=114) group. The FAS and PPS results showed that both groups experienced a median clinical recovery time of three days ($P>0.05$). The median time to defervescence of both groups were 36 hours in FAS and PPS ($P>0.05$), and two groups did not differ in terms of the other secondary endpoints ($P>0.05$). 14 patients (12.39%) in the QXQJ group and 14 patients (12.50%) in the oseltamivir group reported at least one adverse event, respectively. One serious adverse event occurred in the QXQJ group. There was no significant difference in the incidence of adverse events or adverse drug reactions between the groups.

Conclusions: The efficacy of QXQJ oral solution was comparable to that of oseltamivir for treating influenza in children, with an acceptable safety profile.

Trial Registration: Chinese Clinical Trial Registry ChiCTR1900021060.

Keywords: Qinxiang Qingjie oral solution; randomized controlled trial; traditional Chinese herbs; children; influenza

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Introduction

Influenza is an acute contagious respiratory disease caused by influenza viruses and can result in seasonal epidemics and pandemics; thus, it is a serious global health problem (1,2). The influenza A subtypes H1N1 and H3N2 as well as the influenza B subtypes Victoria and Yamagata are the most commonly detected influenza viruses, causing uncomplicated symptoms such as fever (39–40 °C), chills, headache, myalgia, fatigue, and loss of appetite; respiratory-tract symptoms such as cough, sore throat, runny nose, and nasal obstruction may also result (1). Each year, approximately 20–30% of children, the high-risk population for influenza (1,2), experience seasonal influenza epidemics, with an annual infection rate of up to 50% worldwide (3–5). Furthermore, about 30% of children develop influenza complications, with children under the age of five years old and infants under the age of two years old at an increased risk of developing severe cases with complications (2,6). Evidence has demonstrated that influenza accounts for 10–15% of pediatric hospitalizations each year, resulting in increased mortality as well as massive social and economic burdens (7). A 3-year epidemiological study conducted in Hong Kong has demonstrated that influenza caused a total of 662–1,046 days of school absence and 214–336 days

of parental work loss per 10,000 children younger than 18 years old per year; moreover, on average, each school-aged child was absent from school for five days due to influenza and the cost of hospitalization due to influenza was \$1,300 per person (8).

Four classes of anti-influenza drugs, including neuraminidase inhibitors, M2 ion channel blockers, hemagglutinin inhibitors, and RNA polymerase inhibitors are available (2,9). However, circulating influenza virus strains have been found to be resistant to M2 ion channel blockers such as amantadine and rimantadine. Meanwhile, there is scant evidence to support the clinical use of the hemagglutinin inhibitor umifenovir in children (1). In China, RNA polymerase inhibitors such as baloxavir and favipiravir are not approved. Although the oral drug oseltamivir is considered a first-line drug and an optimal treatment for pediatric influenza (10), the oseltamivir-resistant seasonal influenza A virus H1N1 has rapidly spread throughout the world (11,12). In addition, oseltamivir causes gastrointestinal, mental, and neurological adverse events, which can result in patient deterioration and death (13–15).

Therefore, the exploration of novel influenza treatments has also gained attention in traditional Chinese medicine

(TCM). The TCM treatment of influenza is multi-pronged, and includes combating influenza viruses, enhancing the immune response, and achieving satisfactory clinical outcomes with less drug resistance and fewer adverse drug reactions (16). Furthermore, TCM has antibacterial, antipyretic, and analgesic properties (16), implying that the development of TCMs for treating influenza in children is clinically significant.

Qinxiang Qingjie (QXQJ) oral solution is a traditional Chinese herb preparation, which is composed of Huang qin (*Radix scutellariae*), Guang huo xiang (Patchouli), Chan tui (*Periostracum cicadae*), Shi gao (*Gypsum fibrosum*), Ge gen (Kudzu Root), Da huang (*Radix et Rhizoma Rhei*), Chi shao (*Radix Paeoniae Rubra*), Ban lan gen (*Radix isatidis*), Jie geng (*Radix platycodi*), Xuan shen (*Radix scrophulariae*), Shan dou gen (*Sophora subprostrata*), and Gan cao (*Radix glycyrrhizae*). It is used for dispersing wind-heat, clearing the internal heat, detoxification, and relieving a sore throat. A previous study has reported antipyretic, analgesic, antitussive, expectorant, anti-inflammatory, and antibacterial effects of QXQJ (17). *In vitro* studies found that patchouli alcohol, polyphenolic compounds from Patchouli and baicalin, Flavonoids-enriched extract from *Scutellaria baicalensis* root could exert some inhibitory effects on the virus. The acute and long-term toxicity reactions suggest that QXQJ has low toxicity and high safety (18). Chinese medicine is multi-component and multi-targeted, acting integrally on the body rather than having a single effect. Compared to western chemical antiviral western chemical antiviral agents, herbal medicine has potential advantages in restoring the body's functional balance and improving overall symptoms with a higher safety profile (19). However, due to the complex composition, the chemical composition and mechanism of action of QXQJ have not been adequately studied. It is widely used to treat upper respiratory tract infections in children with TCM syndromes of both the exterior and interior heat types (20–22). However, there is a lack of scientific evidence supporting the use of QXQJ to treat pediatric influenza. To address this gap, we conducted a randomized, double-blind, double-dummy, positive-controlled, multicenter, noninferiority clinical study comparing the efficacy and safety of the QXQJ oral solution to those of oseltamivir in children with influenza.

We present the following article in accordance with the CONSORT reporting checklist (available at <https://tp.amegroups.com/article/view/10.21037/tp-22-201/rc>).

Methods

General information

From March 2019 to May 2020, this randomized, double-blind, double-dummy, positive-controlled, multicenter clinical trial was conducted in 14 hospitals throughout China in accordance with the Declaration of Helsinki (as revised in 2013) and Good Clinical Practice (23). The study protocol was reviewed and approved by the Ethics Committee of the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine (No. TYLL2018 [Y] 019). All other participating hospitals (Maternity and Child Health Care of Zaozhuang, The First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine, Shanghai Children's Medical Center, Ezhou Central Hospital, The First Affiliated Hospital of Henan University of Chinese Medicine, Shanghai Municipal Hospital of Traditional Chinese Medicine, Handan Hospital of Traditional Chinese Medicine, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Maternal and Child Health Care Hospital of Yuncheng, Taiyuan Maternity and Child Health Care Hospital, Dongfang Hospital Beijing University of Chinese Medicine, Luohe Hospital of Traditional Chinese Medicine, Changzhi People's Hospital) were informed and agreed with this study. All parents/guardians of the patients provided written informed consent before enrollment. Participants over the age of 8 also gave written consent after understanding the risks and benefits of the study.

Participants

The inclusion criteria for eligibility were as follows: (I) aged 1–13 years; (II) met both the diagnostic criteria for influenza (24) and TCM syndromes of the exterior and interior heat types (25); and (III) developed a fever with an axillary temperature of $\geq 38^{\circ}\text{C}$ in 48 hours. The exclusion criteria were as follows: (I) pharyngoconjunctival fever, herpangina, or suppurative tonsillitis; (II) complications of sinusitis, otitis media, bronchitis, or pneumonia; (III) severe or critical influenza; (IV) received antiviral drugs within 48 hours prior to enrollment; (V) received an influenza vaccination within 12 months before enrollment; (VI) currently receiving systemic corticosteroids or immunosuppressive therapy; (VII) history of epilepsy, febrile convulsions, or recurrent respiratory infections; (VIII) severe malnutrition or rickets, or severe primary heart, brain, liver, kidney, or hematopoietic disease; (IX)

allergic to the study drugs or prone to develop allergic reactions (allergic to ≥ 2 foods or drugs); and (X) lost to follow-up.

Sample size

This trial aimed to add a new functional specialty of QXQJ. According to the Drug Registration Regulation issued by National Medical Products Administration in 2007, the sample size of each group must be at least 100 cases. We finally designed to enroll 240 patients, with 120 for each group, considering a dropout rate of 20%.

Randomization, allocation concealment, and blinding

A random sequence with a 1:1 allocation ratio to the QXQJ or oseltamivir group was generated using SAS software (SAS Inc., Cary, NC, USA). The clinical setting was considered as the stratification factor. Personnel unrelated to this clinical trial performed the randomization procedures, assigned the participants, and prepared the random codes and emergency letters. After the medications were coded, they were sealed and blindly stored until completion of the study. All patients, investigators, and statisticians were unaware of the group assignment. The first unblinding was performed after verifying and locking the database, and the second unblinding occurred following the completion of the statistical analysis report. The investigators properly retained the emergency letters distributed to the centers along with the medications. Only in an emergency, when the participant's medication situation required clarification, could the blinding be uncovered urgently. Following the opening of the emergency letter, the signer, the date of the opening, and the reason for the opening needed to be indicated.

After producing the placebo, the sponsor invited some people to taste whether it was difficult to distinguish between the placebo and the herbal and control drugs. We used the same packaging and coded the medications according to a random number table. Researchers dispensed the medicines in order during the trial. The blinding code was managed by third-party personnel not involved in test trials. After the study was completed, we confirmed the integrity of the blinding code and checked if the emergency letters had been opened illegally.

Interventions

The corresponding simulants were prepared consistently

with QXQJ and oseltamivir in terms of the appearance, odor, and taste. Sucrose and purified water were used to make the QXQJ simulant. Sucrose, sodium carboxymethyl cellulose, and purified water were the components of the oseltamivir simulant. The administered doses of QXQJ and the corresponding simulant were as follows: 10 mL for children aged 1–2 years old, 15 mL for those aged 3–6 years old, and 20 mL for those aged 7–13 years old; four times daily for children with a fever or three times daily when the children were fever-free, for five days. Oseltamivir phosphate granule and the corresponding simulant were administered based on body weight: 30 mg (≤ 15 kg), 45 mg (15–23 kg), 60 mg (23–40 kg), and 75 mg (>40 kg or age ≥ 13 years old); orally twice daily for 5 days.

Guangzhou ApicHope Pharmaceutical Co., Ltd., Guangdong, China, provided the study interventions, which were distributed through each setting's central pharmacy.

Protocol

The study was divided into two phases: a 5-day treatment period and a 2-day medical observation period. The participants were assigned randomly to receive either QXQJ oral solution or oseltamivir, but no other specific influenza medications or therapies were allowed, with the exception of physical cooling. For patients with an axillary temperature of >38.5 °C, paracetamol was prescribed at a maximum dose of 10 mg/kg every 4–6 hours, as needed, and no more than four times daily with the investigator's consent. If the fever persisted, additional antipyretic and analgesic medications could be prescribed. In the case report forms and the medical records, the generic names, administration times, dosages, and reasons for prescribing the concomitant medications were recorded. The follow-up visits occurred on days 5 and 7 following treatment initiation. During the medical observation period, the patient diary and the Canadian Acute Respiratory Illness Flu Scale (CARIFS) (26,27) were recorded by the caregivers every 24 hours. In addition, the axillary temperature was measured every 6 hours. We used the verified and adjusted Chinese version of CARIFs in this study (27). The Chinese version of CARIFs differs slightly from the English version in that it includes 16 items covering three domains: symptoms (headache, sore throat, muscle aches or pain, fever, cough, nasal congestion, runny nose, vomiting), function (poor appetite, not sleeping well, irritable/cranky/fussy, feels unwell, low energy, tired, unable to get out of bed), and the

parental impact (crying more than usual, needing extra care, clinging). The 4-point ordinal scale was as follows: 0= none, 1= mild, 2= moderate, 3= severe. Considering the limited comprehension and expression abilities of infants younger than 2 years old, the four items of feels unwell, headache, sore throat, and muscle aches or pain can be evaluated as “do not know” or “not applicable”. The final CARIFS score was calculated by adding the scores of all applicable items.

Efficacy evaluation

The primary study endpoint was the clinical recovery time, defined as complete defervescence for at least 24 hours and a CARIFS symptom dimension score of 0 or 1. The secondary study endpoints were as follows: (I) time to defervescence, defined as the time period during which a participant's axillary temperature dropped to 37.2 °C for the first time in the following 24 hours; (II) incidences of complications (such as sinusitis, otitis media, bronchitis, pneumonia, or hospitalization due to influenza) and severe or critical influenza (24); (III) negative conversion rate, which referred to the rate of conversion to testing influenza negative within five days; and (IV) improvement in the interior and exterior heat types of TCM syndromes. According to the TCM criteria detailed (see [Tables S1,S2](#)), clinical efficacy was classified as clinical recovery, remarkable improvement, effective, or ineffective, using the gradational scoring method (25).

Safety evaluation

Safety profiles, including adverse clinical events and adverse drug reactions, were evaluated by physical examination (body temperature, resting heart rate, breathing rate, and blood pressure), electrocardiogram, and laboratory tests (white blood cell count, red blood cell count, neutrophil %, lymphocyte %, hemoglobin, platelet, C-reactive protein, alanine aminotransferase, aspartate aminotransferase, total bilirubin, gamma-glutamyl transferase, blood urea nitrogen, creatinine, urine white blood cell count, urine red blood cell count, and protein in urine).

Statistical analysis

The software SAS 9.2 (SAS Institute, Cary, NC, USA) was used for all statistical analyses. A P value <0.05 was considered statistically significant. Normally distributed quantitative data were presented as the mean and standard

deviation, and intergroup comparisons were performed by the *t*-test. The analysis of covariance, including the test center, influenza virus strain type, and patient baseline data, was also conducted. Meanwhile, non-normally distributed data were presented as the median and analyzed using the Kruskal-Wallis rank-sum test. Qualitative data were expressed as numbers and percentages and analyzed by the chi-squared test or Fisher's exact test.

Efficacy was assessed by the full analysis set (FAS) and the per protocol set (PPS), whereas safety evaluation was analyzed using the safety set (SS). The last observation carried forward approach was utilized for dealing with missing values in the primary outcome. Considering other factors such as the clinical setting, the Cochran-Mantel-Haenszel chi-squared test was added to the analyses. The Wilcoxon rank sum test was considered when comparing the ranked data in multiple settings. Kaplan-Meier curves of survival data were used to describe the censoring rate and the survival time for both groups, and then the log-rank test was conducted for comparison. The accelerated failure time model was adopted because some important non-treatment factors (such as the clinical setting, baseline characteristics, and the course of disease) had an impact on the primary outcome. According to the minimum information principle, the model with the best fitting degree was chosen to calculate the ratio of the median recovery time between the two groups and the 95% confidence interval (CI). According to a previous study, the median recovery time for children with influenza was four days (101 h) for oseltamivir and less than one day for QXQJ oral solution, indicating that oseltamivir was not inferior to QXQJ (28). Thus, the lower limit of the 95% CI of the median recovery time ratio was set as >0.8.

Results

Baseline characteristics

A total of 231 enrolled patients were randomly assigned to receive either QXQJ oral solution (n=117) or oseltamivir (n=114) from March 2019 to May 2020. As shown in the Consolidated Standards of Reporting Trials (CONSORT) flowchart ([Figure 1](#)), 224 patients were included in the FAS analysis (n=112/group), 212 in the PPS analysis (n=106/group), and 225 in the SS analysis (n=113 for QXQJ, n=112 for oseltamivir). As shown by the consistent results of the FAS and PPS analyses ([Table 1](#)), there were no significant differences in the baseline characteristics

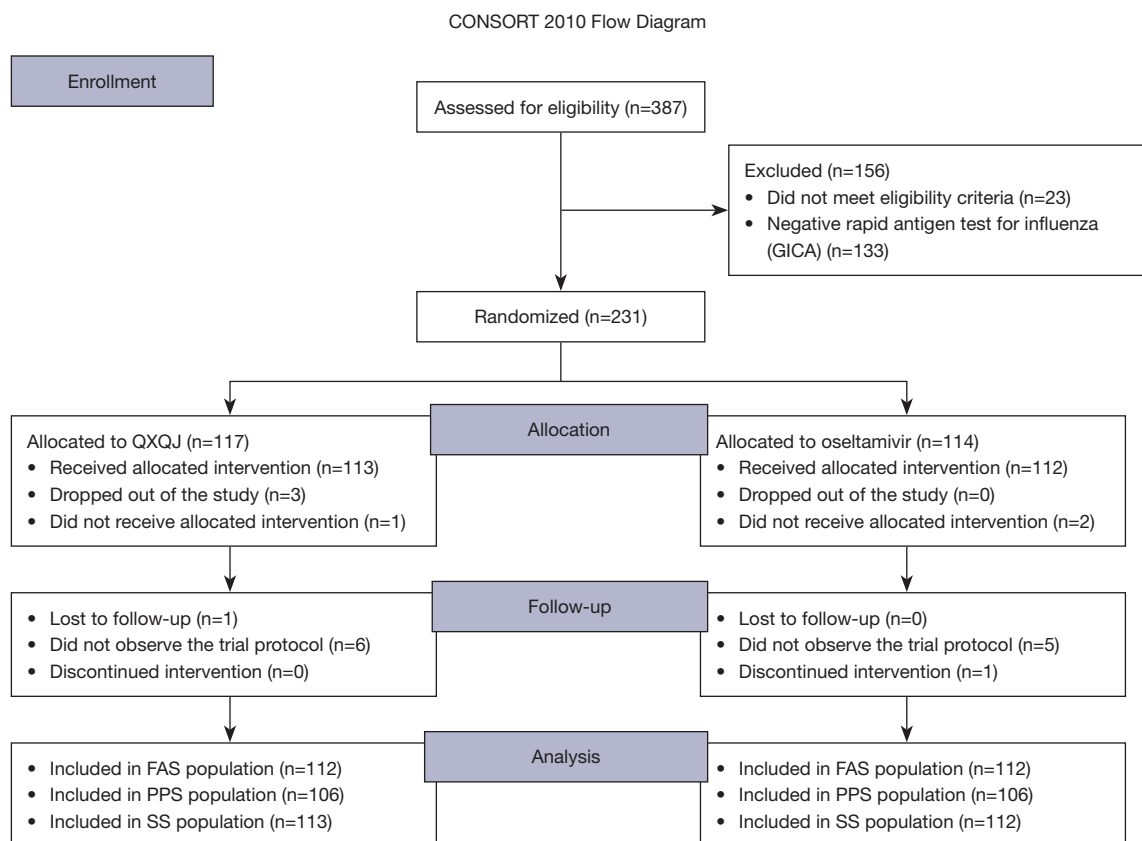


Figure 1 The CONSORT flowchart. CONSORT, Consolidated Standards of Reporting Trials; QXQJ, Qinxiang Qingjie; FAS, full analysis set; PPS, per protocol set; SS, safety set.

between the two groups.

Primary study endpoints

The FAS and PPS results showed that the median clinical recovery time was 3 days in both the QXQJ and oseltamivir groups, with no significant difference (FAS, $P=0.5328$; PPS, $P=0.6995$). Subgroup analyses indicated that the median clinical recovery time for patients with type A (FAS, $P=0.4417$; PPS, $P=0.6818$) or type B influenza (FAS, $P=0.8291$; PPS, $P=0.8674$) was 3 days, with no significant intergroup difference. According to the accelerated failure time-lognormal distribution model, the median time ratio was 0.993 (95% CI: 0.866 to 1.139) for the FAS and 0.983 (95% CI: 0.856 to 1.129) for the PPS, when the clinical setting and disease course were considered. The efficacy of

oseltamivir was not inferior to that of the QXQJ oral liquid with a cut-off value of 0.80 (Table 2 and Figure 2).

Secondary study endpoints

According to the FAS and PPS analyses, the median time to defervescence was 36 hours in both the QXQJ and oseltamivir groups, with no significant difference (FAS, $P=0.2552$; PPS, $P=0.4826$) (Table 2 and Figure 3). The FAS and PPS analyses also showed that the incidence rate of complications was 4.46% and 3.77%, respectively, in the QXQJ group and 0.89% and 0.00%, respectively, in the oseltamivir group, with no remarkable difference (FAS, $P=0.2124$; PPS, $P=0.1215$). There was no severe or critical influenza in either group (Table 2). In addition, the FAS and PPS analyses of the improvement in TCM

Table 1 Baseline characteristics of study subjects

Baseline	FAS analysis			PPS analysis		
	QXQJ (n=112)	Oseltamivir (n=112)	P value	QXQJ (n=106)	Oseltamivir (n=106)	P value
Age, mean±SD, y	7.019±3.025	6.629±2.670	0.3073 ^a	7.043±3.085	6.567±2.654	0.2298 ^a
Height, mean±SD, cm	121.201±20.147	118.605±18.399	0.3151 ^a	121.288±20.214	118.413±18.314	0.2792 ^a
Weight, mean±SD, kg	25.432±10.347	23.836±8.657	0.2118 ^a	25.758±10.497	23.657±8.559	0.1116 ^a
Gender, n (%)						
Male	60 (53.57)	54 (48.21)	0.4226 ^b	58 (54.72)	50 (47.17)	0.2717 ^b
Female	52 (46.43)	58 (51.79)		48 (45.28)	56 (52.83)	
Ethnicity, n (%)						
Han	111 (99.11)	111 (99.11)	1.0000 ^c	106 (100.0)	105 (99.06)	1.0000 ^c
Others	1 (0.89)	1 (0.89)		0 (0.00)	1 (0.94)	
Type A flu, n (%)						
Positive	103 (91.96)	100 (89.29)	0.4917 ^b	99 (93.40)	95 (89.62)	0.3243 ^b
Negative	9 (8.04)	12 (10.71)		7 (6.60)	11 (10.38)	
Type B flu, n (%)						
Positive	11 (9.82)	12 (10.71)	0.8258 ^b	9 (8.49)	11 (10.38)	0.6384 ^b
Negative	101 (90.18)	100 (89.29)		97 (91.51)	95 (89.62)	
Flu classification, n (%)						
A + B	2 (1.79)	0 (0.00)	0.4066 ^c	2 (1.89)	0 (0.00)	0.2706 ^c
A	101 (90.18)	100 (89.29)		97 (91.51)	95 (89.62)	
B	9 (8.04)	12 (10.71)		7 (6.60)	11 (10.38)	
Course of disease, mean±SD, h	19.232±11.641	20.179±13.439	0.5738 ^a	18.868±11.477	20.623±13.629	0.3118 ^a
Pre-diagnostic Tmax, mean±SD, °C	38.887±0.652	38.819±0.586	0.4134 ^a	38.869±0.645	38.822±0.587	0.5783 ^a
Family history, n (%)						
Yes	0 (0.00)	0 (0.00)	–	0 (0.00)	0 (0.00)	–
No	112 (100.0)	112 (100.0)		106 (100.0)	106 (100.0)	
History of allergy, n (%)						
Yes	3 (2.68)	0 (0.00)	0.2466 ^c	2 (1.89)	0 (0.00)	0.4976 ^c
No	109 (97.32)	112 (100.0)		104 (98.11)	106 (100.0)	
Medical history, n (%)						
Yes	1 (0.89)	5 (4.46)	0.2124 ^c	0 (0.00%)	5 (4.72)	0.0596 ^c
No	111 (99.11)	107 (95.54)		106 (100.0)	101 (95.28)	
Pre-diagnostic treatment, n (%)						
Yes	40 (35.71)	47 (41.96)	0.3372 ^b	38 (35.85)	43 (40.57)	0.4797 ^b
No	72 (64.29)	65 (58.04)		68 (64.15)	63 (59.43)	
CARIFS score, mean±SD	21.482±10.285	20.696±7.786	0.5199 ^a	21.594±10.491	20.849±7.779	0.5575 ^a
TCM syndrome score, mean±SD	7.286±2.729	7.482±2.695	0.5884 ^a	7.358±2.751	7.538±2.709	0.6331 ^a

^a, t-test; ^b, χ^2 test; ^c, Fisher's exact test. QXQJ, Qinxiang Qingjie; FAS, full analysis set; PPS, per protocol set; SD, standard deviation; CARIFS, the Canadian Acute Respiratory Illness and Flu Scale; TCM, traditional Chinese medicine; Tmax, maximum temperature.

Table 2 Primary and secondary study endpoints of efficacy

Efficacy outcomes	FAS analysis			PPS analysis		
	QXQJ (n=112)	Oseltamivir (n=112)	P value	QXQJ (n=106)	Oseltamivir (n=106)	P value
Clinical recovery time (days), Med [Q1–Q3],	3 [2–5]	3 [2–4]	0.5328 ^a	3 [2–5]	3 [2–4]	0.6995 ^a
Time to resolution of fever (hours), Med [Q1–Q3],	36 [24–54]	36 [24–54]	0.2552 ^a	36 [24–54]	36 [24–54]	0.4826 ^a
Incidence rate of complications, n (%)	5 (4.46%)	1 (0.89%)	0.2124 ^b	4 (3.77%)	0 (0.00%)	0.1215 ^b
Incidence rate of severe or critical influenza, n (%)	0 (0.00%)	0 (0.00%)	–	0 (0.00%)	0 (0.00%)	–
Improvement in TCM syndromes, n (%)	91 (81.25%)	96 (85.71%)	0.3683 ^c	90 (84.91%)	94 (88.68%)	0.4171 ^c
Difference of TCM syndrome scores before and after treatment, mean ± SD	5.330±3.687	5.563±3.187	0.6147 ^d	5.528±3.623	5.764±3.051	0.6087 ^d

^a, log-rank; ^b, Fisher's exact test; ^c, Wilcoxon rank sum test; ^d, *t*-test. QXQJ, Qinxing Qingjie; FAS, full analysis set; PPS, per protocol set; TCM, traditional Chinese medicine; SD, standard deviation.

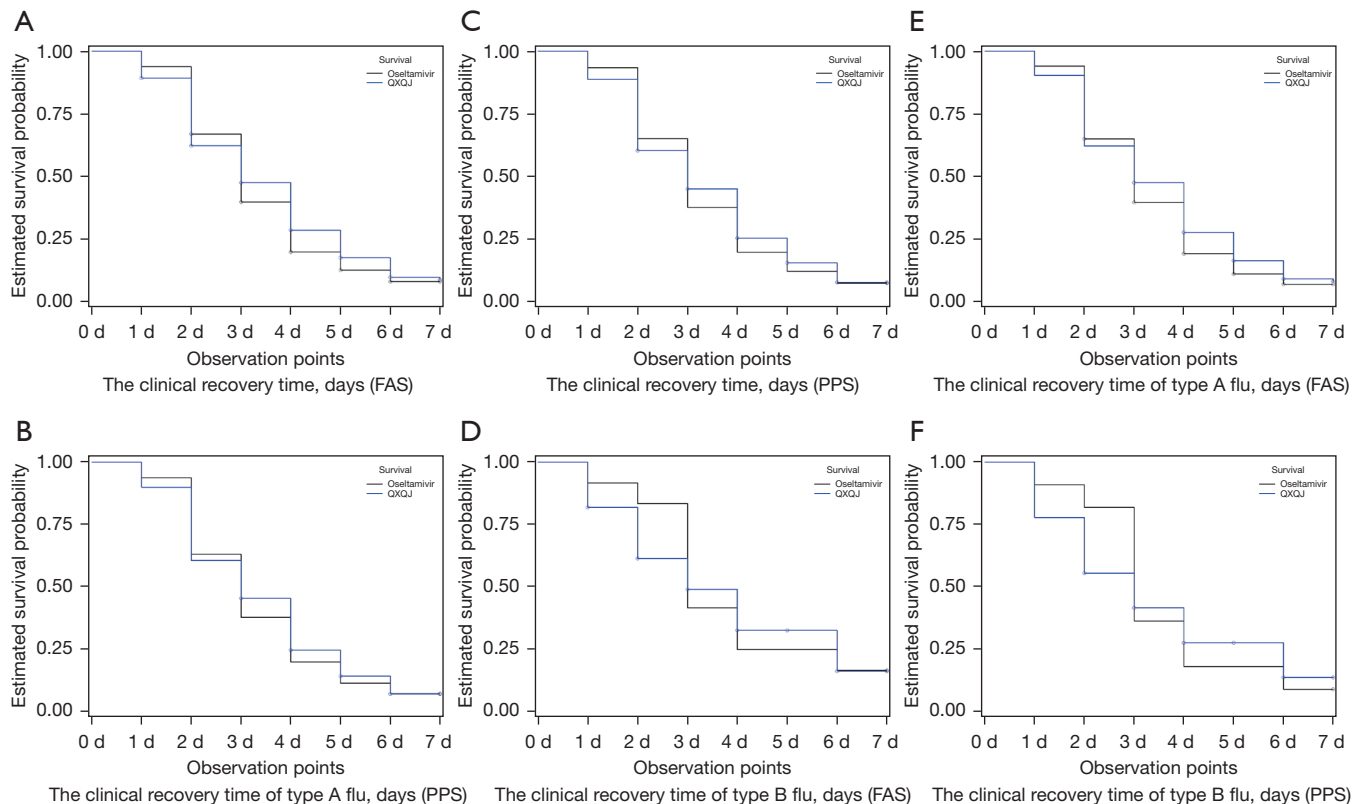


Figure 2 The clinical recovery time (days) in the two groups according to the following analyses: (A) FAS, (B) PPS, (C) FAS of the influenza A virus subgroup, (D) PPS of the influenza A virus subgroup, (E) FAS of the influenza B virus subgroup, and (F) PPS of the influenza B virus subgroup. FAS, full analysis set; PPS, per protocol set.

syndromes revealed that the proportion of patients who reported clinical recovery and remarkable improvement was 81.25% and 84.91%, respectively, for QXQJ and

85.71% and 88.68%, respectively, for oseltamivir, without significant differences (FAS, $P=0.3683$; PPS, $P=0.4171$) (Table 2). Moreover, the FAS and PPS analyses of the

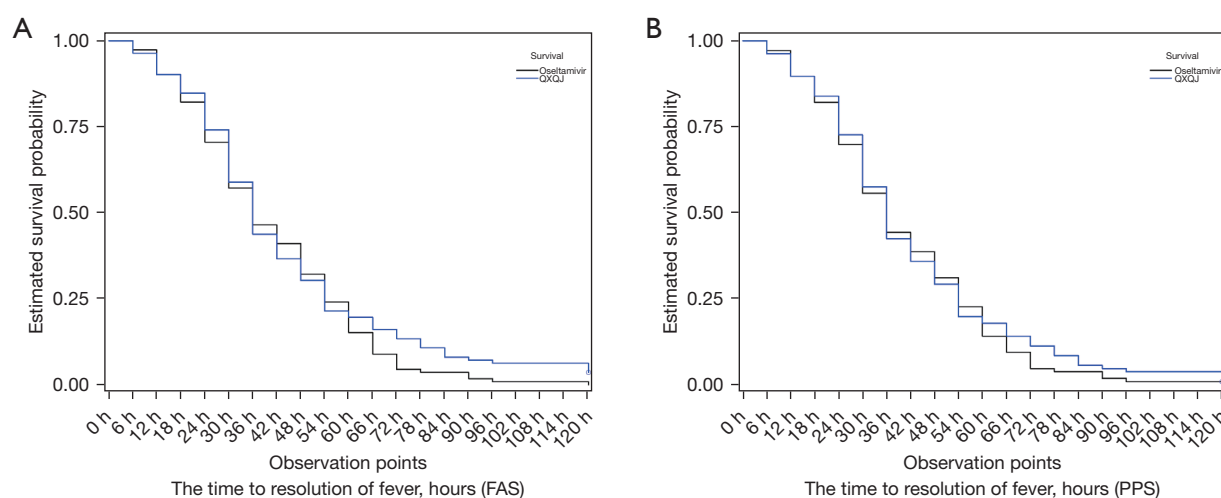


Figure 3 The time (hours) to defervescence in the two groups according to the (A) FAS and (B) PPS analyses. FAS, full analysis set; PPS, per protocol set.

Table 3 Comparison of CARIFs scores between groups

Baseline-to-posttreatment change in CARIFs score	FAS analysis			PPS analysis		
	QXQJ	Oseltamivir	P value ^a	QXQJ	Oseltamivir	P value ^a
Day 1	7.147±10.014	5.198±6.855	0.0931	7.295±10.156	5.472±6.809	0.1268
Day 2	11.926±10.127	10.655±8.750	0.3221	12.125±10.185	10.952±8.768	0.3733
Day 3	15.551±10.745	14.946±8.122	0.6385	15.596±10.853	15.217±7.964	0.7729
Day 4	17.944±10.460	17.648±8.059	0.8165	18.048±10.570	17.798±7.979	0.8475
Day 5	19.467±10.379	18.745±7.961	0.5654	19.519±10.500	18.906±7.889	0.6322
Day 6	20.159±10.331	19.236±7.931	0.4607	20.240±10.441	19.377±7.883	0.4993
Day 7	20.626±10.155	19.627±7.808	0.4168	20.712±10.258	19.726±7.785	0.4334

^a, *t*-test. QXQJ, Qinxiang Qingjie; CARIFs, the Canadian Acute Respiratory Illness and Flu Scale; FAS, full analysis set; PPS, per protocol set.

TCM syndrome scores revealed that the difference of the TCM syndrome scores before and after treatment was 5.330 ± 3.687 and 5.528 ± 3.623 , respectively, in the QXQJ group and 5.563 ± 3.187 and 5.764 ± 3.051 , respectively, in the oseltamivir group, with no significant differences (FAS, $P=0.6147$; PPS, $P=0.6087$) (Table 2). As shown in Table 3, after treatment, there are no significant differences in the changes in CARIFs scores at each visit point relative to their baseline values between groups. Furthermore, there were no significant differences in the proportion of patients testing negative for influenza A or influenza B in both groups, with the FAS and PPS analyses showing comparable results (Table 4).

Safety profiles

A total of 28 adverse events, including vomiting, abdominal discomfort, abnormal blood tests, abnormal liver function tests, and complications, were reported, with 14 (12.39%) in the QXQJ group and 14 (12.50%) in the oseltamivir group. One patient (0.88%) who received the QXQJ oral solution was hospitalized due to a serious adverse event of pneumonia, leading to withdrawal from the study. Four adverse drug reactions were observed, including 1 (0.88%) in the QXQJ group and 3 (2.68%) in the oseltamivir group. The incidences of adverse events, serious adverse events, and adverse drug reactions did not differ significantly between the two groups (Table 5). In addition, there were

Table 4 Swab tests results of the patients

Patients	Database	Results	QXQJ group	Oseltamivir group	P value
Type A flu (positive), n (%)	FAS	1	57 (55.34)	55 (55.00)	1.000
		2	2 (1.94)	1 (1.00)	
		3	44 (42.72)	44 (44.00)	
		Total	103	100	
Type A flu (positive), n (%)	PPS	1	56 (56.57)	52 (54.74)	0.8696
		2	2 (2.02)	1 (1.05)	
		3	41 (41.41)	42 (44.21)	
		Total	99	95	
Type B flu (positive), n (%)	FAS	1	3 (27.27)	6 (50.00)	0.6802
		2	1 (9.09)	1 (8.33)	
		3	7 (63.64)	5 (41.67)	
		Total	11	12	
Type B flu (positive), n (%)	PPS	1	3 (33.33)	6 (54.55)	0.4959
		2	1 (11.11)	0 (0.00)	
		3	5 (55.56)	5 (45.45)	
		Total	9	11	
Influenza (positive), n (%)	FAS	1	58 (51.79)	61 (54.46)	0.8655
		2	3 (2.68)	2 (1.79)	
		3	51 (45.54)	49 (43.75)	
		Total	112	112	
Influenza (positive), n (%)	PPS	1	57 (53.77)	58 (54.72)	0.7739
		2	3 (2.83)	1 (0.94)	
		3	46 (43.40)	47 (44.34)	
		Total	106	106	

1: positive (baseline) – negative (outcome); 2: positive (baseline) – positive (outcome); 3: positive (baseline) – data missing (outcome). QXQJ, Qinxing Qingjie; FAS, full analysis set; PPS, per protocol set.

Table 5 Safety profile

Safety outcomes	SS analysis		
	QXQJ (n=113)	Oseltamivir (n=112)	P value
AE, n (%)	14 (12.39)	14 (12.50)	0.9799 ^a
SAE, n (%)	1 (0.88)	0 (0.00)	1.0000 ^b
ADR, n (%)	1 (0.88)	3 (2.68)	0.3694 ^b

^a, χ^2 test; ^b, Fisher's exact test. AE, adverse event; SAE, serious adverse event; ADR, adverse reaction; SS, safety set; QXQJ, Qinxing Qingjie.

no significant differences in vital sign changes or laboratory test results, with the exception of the platelet count normal/abnormal (baseline)—abnormal (outcome) rate, which was 25% in the oseltamivir group and 10.48% in the QXQJ group ($P=0.006$).

Discussion

In this clinical trial, we demonstrated that QXQJ was comparable to oseltamivir in terms of efficacy and safety

for treating pediatric influenza. This study employed both TCM syndrome scores and laboratory test results to investigate the efficacy of a TCM in a quantitative and comprehensive manner. Our results showed that the clinical recovery time for both the QXQJ and oseltamivir groups was three days, with no significant differences in the incidence of complications, cases of severe or critical influenza, or negative conversion. Moreover, QXQJ oral solution was as safe and acceptable as oseltamivir in terms of adverse events, serious adverse events, and adverse reactions. Both groups experienced common clinical complications associated with influenza, including otitis media, bronchitis, and pneumonia. Due to their immature immune development, children are more susceptible to complications than adults, which suggests that they should be treated for influenza as soon as possible to minimize the risk of complications.

Favorable effects of QXQJ have been extensively reported. A previous pharmacodynamic study demonstrated that the QXQJ oral solution inhibits influenza virus proliferation in chicken embryos at a minimum inhibitory concentration of 0.062 g/mL, indicating its inhibitory effect on viral replication. In addition, QXQJ may reduce the release of inflammatory mediators, thereby lowering cytokine levels and regulating immunity (17). Besides, patchouli alcohol, a monomer derived from patchouli, has been shown to have activities against influenza virus *in vitro* (29). Similarly, Wu *et al.* reported that patchouli downregulates the expression of inflammatory cytokines such as interferon- γ (IFN- γ) and interleukin-4 (IL4) (30). According to Liu *et al.*, polyphenolic compounds isolated from patchouli may have potential as novel anti-influenza agents due to their neuraminidase inhibitory activity (31). *Radix scutellariae*, another component of the QXQJ oral solution, has been confirmed to protect influenza A virus-infected mice by inhibiting neuraminidase activities and remarkably decreasing lung virus titers (32). Another study revealed that *Radix scutellariae* extracts, namely, baicalin, baicalein, wogonin, chrysin, and oroxylin A, have lower half-maximal inhibitory concentration values than oseltamivir phosphate and that free flavonoids exhibited greater anti-H1N1 effects than O-glycosides and C-glycosides (33). Other ingredients of the QXQJ oral solution have been reported to help patients recover from the flu by inhibiting neuraminidase, attenuating the expression of IL6, reducing reactive oxygen species and nitric oxide production, imposing antipyretic effects, and promoting blood circulation (34-37).

Previous randomized controlled trials have explored the roles of several TCMs, for example, Antiwei granules, Maxingshigan, and Yinqiaosan ban lan gen granules, in the treatment of influenza when compared with placebo and oseltamivir (38-40). These results demonstrate the benefits of TCMs in fever resolution, symptom relief, and flu recovery. As opposed to antiviral drugs like oseltamivir, the clinical value of TCM lies in a comprehensive treatment of influenza from multiple targets and multiple levels. The main objective is to shorten the course of the disease, which is why clinical recovery time is the prime indicator of this medicine, while virological indicator is an important secondary indication. This is the first study to examine the efficacy and safety of QXQJ in children with influenza by introducing a double-dummy technique to enhance clinical operability and minimize bias. In addition, we considered the clinical recovery time together with TCM syndrome scores, creating an objective and comprehensive evaluation system for efficacy. However, several limitations should be acknowledged. For example, there was no placebo-controlled group to evaluate the absolute efficacy of this trial. There are several reasons for not using a placebo control in this study. At first, oseltamivir phosphate remains the first-line treatment option and a recognized positive control drug according to pediatric influenza guidelines in both China and USA. Second, Chinese parents have a low acceptance for placebo, making it difficult to recruit study participants. Furthermore, children are more susceptible to flu complications and severe illness. According to basic medical ethics principles, the use of placebos does not aid in the clinical recovery of children with influenza. Moreover, some participants failed to completely recover by the endpoint of this study due to the short observation period. Although throat swabs were collected from all patients at baseline, only 124 (55.36%) patients had their throat swabbed at the study endpoint. Considering that most children resist the throat swab examination, this study did not force children to undergo sample collection following treatment, resulting in missing data. However, the virus negative conversion rate is a secondary indicator that has no bearing on our primary conclusions.

Conclusions

This study found that the QXQJ oral solution and oseltamivir are equally effective and safe for the treatment of influenza in children.

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Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at <https://tp.amegroups.com/article/view/10.21037/tp-22-201/rc>

Trial Protocol: Available at <https://tp.amegroups.com/article/view/10.21037/tp-22-201/tp>

Data Sharing Statement: Available at <https://tp.amegroups.com/article/view/10.21037/tp-22-201/dss>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tp.amegroups.com/article/view/10.21037/tp-22-201/coif>). All authors report that this study was funded by Guangzhou ApicHope Pharmaceutical Co., Ltd. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and Good Clinical Practice. The study protocol was reviewed and approved by the Ethics Committee of the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine (No. TYLL2018 [Y] 019). All the other participating hospitals (Maternity and Child Health Care of Zaozhuang, The First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine, Shanghai Children's Medical Center, Ezhou Central Hospital, The First Affiliated Hospital of Henan University of Chinese Medicine, Shanghai Municipal Hospital of Traditional Chinese Medicine, Handan Hospital of Traditional Chinese Medicine, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Maternal and Child Health Care

Hospital of Yuncheng, Taiyuan Maternity and Child Health Care Hospital, Dongfang Hospital Beijing University of Chinese Medicine, Luohe Hospital of Traditional Chinese Medicine, Changzhi People's Hospital) were informed and agreed with this study. All parents/guardians of the patients provided written informed consent before enrollment. Participants over the age of 8 also gave written consent after understanding the risks and benefits of the study.

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Table S1 The treatment observation period was 5±1 days after medication, and the follow-up was at 7 days after medication

Item	Research phase		
	Baseline day -1 to day 0	Treatment and follow-up	
		Treatment observation period (5 ± 1 days after medication)	Follow-up (7 days after medication)
Screening and recruitment	×		
Signed informed consent	×		
Throat swab influenza virus detection: colloidal gold method	×		
Throat swab influenza virus detection: RT-PCR method	×	×	
Serum influenza virus IgM antibody detection	× [#]	× [#]	
Record general information	×		
Physical examination	×	×	
CARIFS scores		The caregivers of the children filled out the diary card and recorded the CARIFS score every 24 h	
The efficacy of TCM syndromes scale	×	×	
Blood and urine routine	×	×	× [*]
CRP	×	×	× [*]
ECG	×	×	× [*]
Myocardial enzymes	× [#]	× [#]	× [*]
Liver and kidney function	×	×	× [*]
Distribution and recovery of trial drugs	×	×	
Issuance and recovery of patient diary	×	×	×
Records of concomitant medications	×	×	×
Adverse events evaluation		×	×
Summary of the trial		×	×

Note: ×[#]Optional items; ×^{*}Follow-up until patients returned to the normal or baseline value

Table S2 Scores for syndromes of heat in both the exterior and interior

Syndromes	Level			
	(-)	(+)	(++)	(+++)
Main symptoms	Score of 0	Score of 2	Score of 4	Score of 6
Fever	The highest axillary temperature was $\leq 37.2^{\circ}\text{C}$ (24 h before consultation)	The highest axillary temperature was $37.3\text{--}37.9^{\circ}\text{C}$ (24 h before consultation)	The highest axillary temperature was $38\text{--}39^{\circ}\text{C}$ (24 h before consultation)	The highest axillary temperature was $>39^{\circ}\text{C}$ (24 h before consultation)
Constipation	/	Cracks on stool surface	Bumps on stool surface	Stool shape is like a hard ball
Other symptoms	Score of 0	Score of 1	Score of 2	Score of 3
Aversion to cold	/	Slightly feel the wind and cold and snuggle up in the mother's arms	Feel wind and cold and need to wear a quilt	Feel wind and cold and a quilt is not sufficient
Stuffy nose	/	Slight nasal congestion that does not affect breathing	Nasal congestion	Stuffed nose and patients need to open mouth to breathe
Runny nose	/	The snot is white and turbid, in a small amount	The snot is white and turbid, in a large amount	The snot is yellow and turbid, in a large amount
Pharyngeal swelling and pain	/	Slightly congested pharynx, no pain or slight pain	Pharyngeal congestion and edema, with pain when swallowing	Pharyngeal congestion and edema, severe sore throat, with a difficulty of swallowing
Cough	/	Occasional cough	Intermittent cough that does not affect rest and sleep	Frequent coughing day and night that affects rest and sleep
Thirst	/	Slightly thirsty	Thirsty and dry throat	Polydipsia
Irritability	/	Occasional	Often	Day and night
Tongue vein	Record, no score			
Tongue image	<input type="checkbox"/> Red tongue, with thin yellow or yellow coating		<input type="checkbox"/> Others:	
Pulse condition	<input type="checkbox"/> Floating pulse and purple fingerprint		<input type="checkbox"/> Others:	