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Treatment effectiveness of two Chinese herbal medicine formulae in upper respiratory tract infections—a randomized double-blind placebo-controlled trial

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Aim and objectives. To study the effect of two Chinese herbal medicines (CHMs) formulae in treating acute upper respiratory tract infections (URTIs), diagnosed by Traditional Chinese medicine (TCM), compared to placebo.

Design. Two randomized, double-blind placebo-controlled trials nested in a study of 327 patients who were diagnosed with URTIs in Hong Kong. Subjects were classified into one of two TCM syndrome groups by a Chinese medicine practitioner and randomized to receive the corresponding CHM formulae or placebo up to maximum of 10 days. The proportions of patients who had resolution of illness on Days 4 and 7 were the primary outcomes. The duration of symptom resolution, health-related quality of life scores measured by the SF-36 and ChQOL, and adverse effects were secondary outcomes.

Results. There was no statistically significant difference between the treatment and placebo in resolution rates at Day 4 or 7. The mean time of resolution of symptoms was Day 10, for either wind-cold or wind-heat syndrome. Both patients in treatment and placebo had significantly improved in health-related quality of life with time, but patients in wind-cold group had significantly more improvement in the SF-36 general health score ($P = 0.01$) than placebo.

Conclusions. Two CHM formulae commonly used for URTIs were not found to be more effective than placebo in either cure or reduction of symptoms of URTIs. However, Jing Fan Bai Du san might be able to improve general health more than placebo for patients with wind-cold syndrome. Both formulae were not associated with any more side effects.

Keywords. Chinese medicine, family medicine, infectious diseases, randomized controlled trial, respiratory medicine, multidisciplinary care.

Introduction

There is no established curative treatment in Western medicine for upper respiratory tract infections (URTIs) except for selected cases of influenza. Studies have shown that the average duration of illness of an URTI is around 7 days[1] and most URTIs resolve by the 10th day.[2] Chinese herbal medicine (CHM) is commonly used by people in Hong Kong on its own or along side with Western medicine for the treatment of URTIs and this is also increasing in Western countries. However, the scientific evidence to support its use is not sufficient. Only a few CHM have been proven by randomized controlled trial (RCT)[3] with most claims based on empirical experience leads to conclusion that CHM was not effective or even harmful.[4] Even though RCTs conducted on Traditional Chinese medicine (TCM) were rated to be poor in quality,[5–8] classical RCT enforced the evaluation of TCM by the conventional Western medicine model was found to be impractical and inappropriate.[9]

The inappropriateness of classical RCT to evaluate TCM led to the development of an alternative clinical trial method: the pragmatic design with prior randomization by Fitter[10] classifies eligible patients into syndrome groups by TCM practitioners before they are randomized to receive the appropriate treatment or placebo. A study showed the pragmatic design, integrating of the CMP's syndrome differentiation based on TCM theory into a RCT, was feasible in an

acupuncture clinical trial.[11] This model was also used successfully in an RCT on the treatment of irritable bowel syndrome with CHM showing better improvement in patients treated with individualized Chinese herbal formulae than standard TCM treatment and placebo groups.[12] This method has been recommended by the Medical Research Council in the UK,[13] the NIH in the USA[14] and WHO[15] which have further established guidelines on the research methodology for evaluating the effectiveness of complementary and alternative medicine for attaining evidence-based TCM[16,17] is the global trend.

Acute URTIs are rarely lethal but are the most common illnesses encountered in primary care.[18] WHO has pointed out that URTIs have a great impact on personal and economic aspects[19] as it accounts for ~100 million visits per year in the USA.[20] Sixty per cent of the working adults in Hong Kong have contracted URTIs with a mean loss of 8.8 days of perfect health per worker and a total loss of up to HK$ 31.3 billion of economic output each year.[21]

URTIs mainly can be differentiated into two types according to the theory of TCM: wind-cold syndrome and wind-heat syndrome[22] which leads to the use of two traditional Chinese herbal formulae: the Jing Fang Bai Du san (荊防敗毒散) for the wind-cold syndrome and the Ying Qiao san (銀翹散) for the wind-heat syndrome.[23] Jing Fang Bai Du san and Ying Qiao san are available over-the-counter in Mainland China and Hong Kong. These two formulae are the standard treatments recommended by the Chinese National Guidelines for Chinese Medicine Practitioners (CMPs).[24,25] Although no serious adverse reactions have ever been reported, data on the side effects of these CHM formulae are scanty, except mild diarrhoea and headache have been associated with their intake.[26]

Although there are data suggesting the effectiveness of these two formulae for URTIs, most of the previous studies were observational and the few clinical trials were of questionable quality.[27] Furthermore, the results of trials conducted at Mainland China may not be generalizable to Hong Kong.[28] The aim of this study was to test whether treatment with Jing Fang Bai Du san or Ying Qiao san, guided by TCM diagnosis in advance, would significantly increase recovery rate, minimize the duration and/or severity of symptoms or improve quality of life of patients with URTIs compared to placebo in primary care.

Methods

Design and subjects

Since URTIs are classified into two distinct groups in TCM to be treated by completely different CHM formulae, this study was designed to as two nested randomized, double-blind placebo-controlled trials according to the subject's TCM syndrome diagnosis. All adult patients diagnosed to have URTIs by Western medicine doctors in two public primary care outpatient clinics in Hong Kong from October 2006 to June 2007 were invited by the consulting doctors. Each patient who agreed to participate was referred to the CMP for further assessment for eligibility. The inclusion criteria were (i) aged ⩾18 years, (ii) had developed URTIs for ⩽48 hours, (iii) had at least one symptom of infection (i.e. general malaise, headache, chills, muscle ache, feverishness or an oral temperature >37.5° C) and (iv) one symptom of upper respiratory tract (i.e. cough, hoarseness, running nose, nasal obstruction, itchy throat, sore throat or sneezing). Subjects were excluded if their URTIs were with medications other than antihistamine, paracetamol, lozenges and/or nasal decongestants; they were pregnant or breastfeeding; they had a history of cancer, liver disease, diabetes mellitus, immunodeficiency, asthma, allergic rhinitis, cystic fibrosis or chronic bronchopulmonary diseases, drug or alcohol abuse or allergy to food additives or the study medications or they were taking chronic medication of any kind of herbs. Written informed consent was obtained from each subject.

Sample size determination

Based on previous studies showing that these CHM formulae were associated with 20%–70% higher rates of improvement or resolution of URTIs compared with placebo or Western medicine after 7 days of treatment.[29,30] Thus, we expected at least 20% difference in resolution rate between a Herbal Formula (A or B) and the corresponding placebo group. With 5% false positive error rate, 82 patients in each treatment group for Group A or B patients were needed in order to have 80% power by a Fisher's exact test. Hence, we recruited 164 patients with wind-cold syndrome and 164 patients with wind-heat syndrome.

Randomization and interventions

The registered CMP assessed the subject to confirm that the symptoms satisfied the TCM diagnosis of URTIs and further categorized them into wind-cold (n = 162) or wind-heat syndrome (n = 165). At the time of enrolment, each subject completed a structured questionnaire on socio-demographics, the frequency of URTIs, chronic morbidity and personal or household smoking, the Chinese (HK) SF-36 Health Survey-acute version[31] and the Chinese Quality of Life Instrument [ChQOL (HK version)].[32] The symptoms of the patients were recorded and their severity was rated on a 10-point scale.

Wind-cold syndrome (Group A) patients were randomized to receive Jing Fan Bai Du san or placebo while wind-heat syndrome (Group B) patients were randomized to receive Ying Qiao san or placebo. For each patient group, a randomization table matching patients'

recruitment number to the medication number was generated by block randomization in a computer. The randomization was done by a statistician who did not take part in any patient recruitment or assessment.

The Jing Fang Bai Du san (荊防敗毒散) formula claims to relieve external symptoms and effectively clear up the pathogenic cold. It contains 13 herbs including, Radix Angelicae Pubescentis (獨活), Radix Peucedani (前胡), Radix Ginseng (人參), Smilacis Glabrae Rhizoma (茯苓), Rhizoma Chuanxiong (川芎), Fructus Aurantii (枳殼), Radix Platycodi (桔梗), Radix Glycyrrhizae (甘草), Herba Schizonepetae (荊芥), Fructus Arctii (牛蒡子), Menthae Folium (薄荷), Radix Saposhnikoviae (防風), Rhizoma et Radix Notopterygii (羌活). Pharmacological studies have shown that this formula could effectively inhibit the activities of streptococcus-induced inflammation.[33] Previous clinical studies showed mixed results on its effectiveness.[29,30] One study showed that it was no better than no treatment,[29] while another study showed Jing Fang Bai Du san (荊防敗毒散) that concentrated granules were more effective (80%) than Western medicine (10%) in improving and resolving symptoms of wind-cold syndrome within 7 days.[30]

Ying Qiao san (銀翹散) claims to relieve external symptoms and effectively clear up the pathogenic heat. It contains 10 herbs: Fructus Forsythiae (連翹), Flos Lonicerae (銀花), Radix Platycodi (桔梗), Folium Menthae (薄荷), Radix Glycyrrhizae (甘草), Herba Schizonepetae (荊芥), Sojae Semen praeparatum (淡豆豉), Fructus Arctii (牛蒡子), Phragmitis Rhizoma (蘆根) and Herba Lophatheri (竹葉). Pharmacological studies showed anti-inflammatory, antipyretic, analgesic, anti-bacterial and antiviral actions.[34] A clinical trial showed that Ying Qiao san (銀翹散) concentrated granules were more effective (66.13%) than Western medicine (40%) in resolving the symptoms of wind-heat syndrome within 1 week.[35]

The CHM preparations and placebo were supplied by a local pharmaceutical company that manufacture these two CHM formulae in the form of concentrated granules for sale to hospitals and over-the-counter in Hong Kong. These granules are extracted from the Chinese herbs of the specific formulae replicating the traditional method of preparing decoction using modern extraction and concentration technologies, according to the Good Manufacturing Practice (GMP) standards. All granules were chemically standardized, granule size and weight in each sachet were carefully calibrated and quality assured for solubility and stability. Dosing instructions were based on the recommendations of the manufacturer (Two 7-g sachets two times daily). Both the CHM formulae and placebo were packed in identical sachets that were labelled with the medication randomization numbers only. The CHM formulae and placebo granules were identical in appearance and colour. A flavour was added to the placebo to mimic that of herbs. The CMP was unable to differentiate between them. Both the subjects and the CMP who assessed the subjects were blinded to the nature of the treatment. The supplier kept the medication and placebo codes, which were to be broken at the end of the study after completion of all the assessments and data analysis or when there was a severe adverse event.

Each subject was given 22 sachets of the allocated treatment and asked to dissolve one sachet in warm water to drink it two times daily. Subject could continue with the treatment prescribed by their consulting Western medicine doctors but were recommended to take the Western medicine and the study treatment 2 hours apart. The study treatment should be continued until all symptoms had resolved or up to a maximum of 10 days. All subjects were asked not to take any other medications except the ones prescribed by the consulting Western medical doctor and their long-term medications. Patients were asked to complete a diary documenting the severity of symptoms and timing of taking their study treatment and Western medicines for as long as 21 days.

Follow-up assessments

All subjects were contacted by telephone on Days 1, 4, 10, 14 and 20 to assess their symptoms and to find out if they had developed any side effects or adverse reactions. On Day 7 post-treatment, all subjects returned to the clinic for a follow-up assessment by the CMP. The number of sachets was counted, the URTI symptoms and treatment side effects were evaluated and the Chinese (HK) SF-36 Survey and ChQOL (HK version) were administered again in the follow-up visits. The subjects were asked to return all the unused granules sachets and diary to the investigators by post in a pre-paid envelope after 21 days.

Outcome measures and data analysis

The primary outcome was the proportion of patients resolved from URTIs. URTIs resolution was defined as the resolution of all symptoms (i.e. a Score 0 or 1 in all symptoms). Secondary outcomes included the number of days from the onset of illness to resolution, change in daily total symptom score, the area under the curve (AUC) of the total daily symptoms score, changes in the SF-36 scores, ChQOL scores, number of days absent from work or school and the incidence of adverse effects.

The difference in the proportions of patients who had resolution of URTIs symptoms between the treatment and placebo groups were analysed separately for patients with wind-cold syndrome and patients with wind-heat syndrome by a Fisher's exact test. The intention-to-treat (ITT) principle was used when all missing values were substituted by the last observed value. The analysis was also performed on patients

with complete measurements to assess the impact of missing values. The final conclusions were, however, made from results derived by the ITT principle.

The AUC of the total symptom score over the 21 days between the treatment group and corresponding placebo groups was compared by simple regression analysis with checking of model adequacy by examining the standardized residuals. A stepwise forward Cox regression analysis was performed for predicting variables for the resolution of URTIs symptoms by entering independent variables, including treatment (CHM versus placebo), baseline symptom score, socio-demographic characteristics and use of Western medications. URTI symptom resolution was defined as the resolution of all symptoms (i.e. a score of <2 in each of the symptoms) or no resolution (any symptom score >1).

The change in total symptom score, the SF-36 scores and the ChQOL scores over time were assessed and compared between the treatment and placebo groups by two-sample *t*-tests by linear mixed effects model with random intercept and group as fixed factor. The occurrence of side effects was compared between the treatment and placebo groups by Fisher's exact test. Some patients were found to have taken Western medicine. A sensitivity analysis after removing these patients was performed to assess the impact of the use of Western medicine on the treatment effects.

A 5% level of significance was used in all significant tests and the analysis was performed in the SPSS Version 17.

Results

Subjects

A total of 327 subjects were recruited with 162 and 165 patients wind-cold and wind-heat syndrome, respectively. In the wind-cold syndrome group, 153

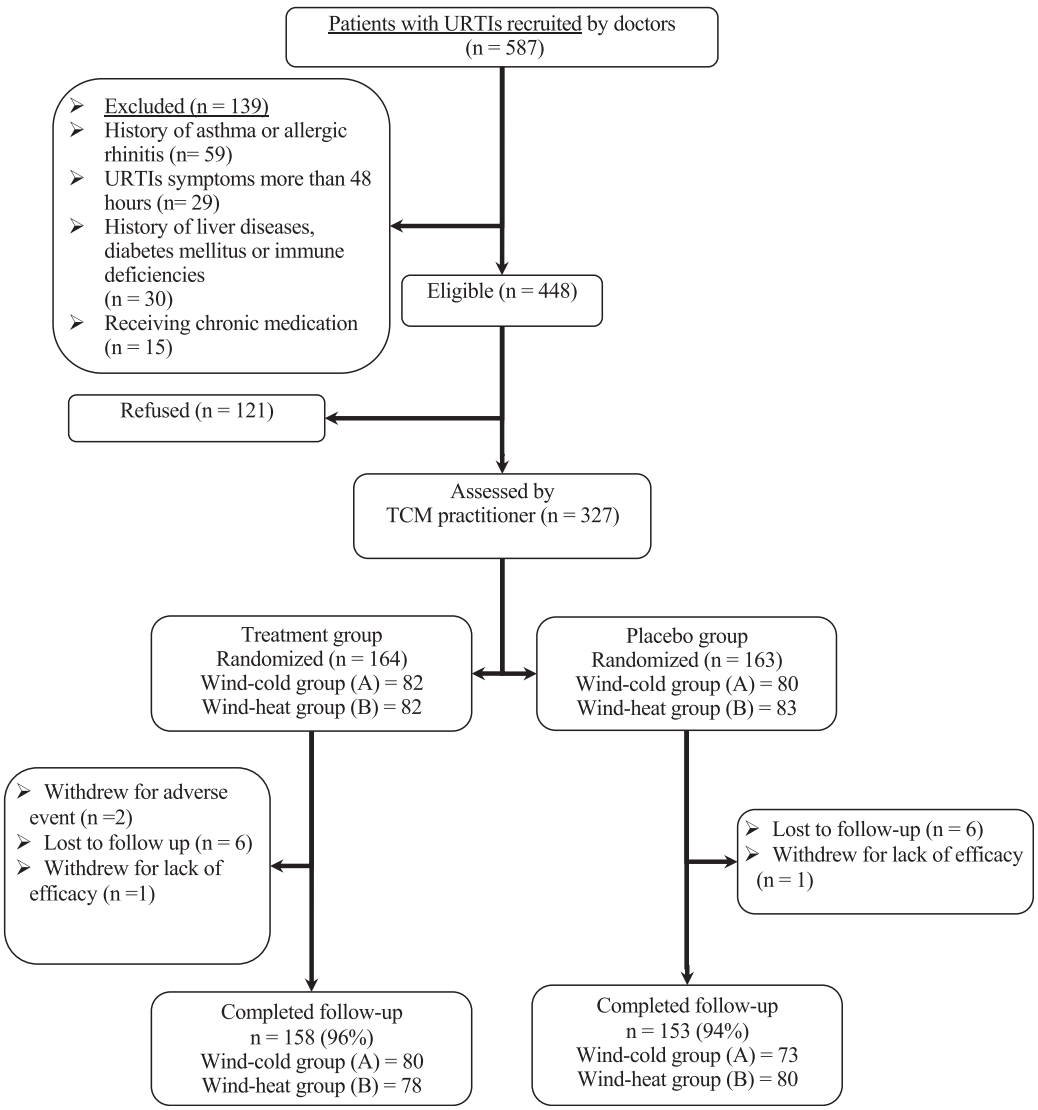

FIGURE 1 *Patient randomization and follow-up flow chart*

(94%) completed the study. In the wind-heat syndrome group, 158 (96%) patients completed the study (Fig. 1). Twelve patients were lost to contact, two patients withdrew from the treatment on Day 2 because they thought the treatments were ineffective and two patients withdrew from the trial because of adverse effects that subsided immediately after the medication was stopped. Compliance with study medication was high as measured by patient report and by sachets counts (72.0% for wind-cold treatment, 62.5% for wind-cold placebo, 85.4% for wind-heat treatment and 78.3% for wind-heat placebo).

Patient baseline characteristics are shown in Table 1. There were no significant differences between treatment and placebo groups in socio-demographic distributions, the mean number of URITs contracted in previous year, smoking history or severity of symptoms.

Symptoms resolution. Overall, 70% and 90% of patients had complete resolution of symptoms on Day 10 and Day 21, respectively. There was no statistically significant difference between the treatment and placebo groups in individual symptoms or days with complete symptom resolution overall or by wind-cold or wind-heat syndrome groups (Table 2). The proportion of patients' resolution did not reach any statistical significance between treatment or placebo groups. Most symptoms resolved in a median of 3 days and completely subsided by Day 10. Cough was the symptom that persisted for the longest with a median of 4 days (Table 3). But 7.2% of patients in the treatment group still had cough by Day 21. Sensitivity analysis with inclusion of only subjects who completed the follow-up also showed similar results.

Cox regression analysis (Table 4) showed that the resolution of URTIs symptoms was significantly associated with age ($P = 0.04$), not taking Western medication on baseline ($P = 0.02$), daily total symptoms score at baseline ($P = 0.00$) and proportion of days taking Western medication during the period from baseline

TABLE 1 *Baseline characteristics of study subjects*

	Treatment group			Placebo group		
	All	Wind-cold syndrome ($n = 82$)	Wind-heat syndrome ($n = 82$)	All	Wind-cold syndrome ($n = 80$)	Wind-heat syndrome ($n = 83$)
Mean age (years/SD)	44.2 (11.1)	44.4 (11.7)	44.3 (10.4)	43.5 (11.5)	42.0 (11.5)	44.3 (11.5)
Range	20–77	22–77	20–71	18–74	20–73	18-74
Gender, (%)						
Female	49.4	51.2	46.3	53.6	56.3	51.8
Male	50.6	48.8	53.7	46.4	43.7	48.2
No. of URTIs in the previous year, mean	4.2	4.4	4.0	3.7	3.4	4.0
Smoking history (%)						
Never smoked	87.2	86.6	87.8	81.6	85.0	78.3
Current smoker	7.3	4.9	9.8	12.9	10.0	15.7
Previous smoker	5.5	8.5	2.4	5.5	5.0	6.0
Mean daily total symptoms score	26.9 (13.1)	26.6 (14.5)	27.2 (11.7)	27.3 (13.6)	27.1 (14.1)	27.4 (13.3)
ChQOL						
Physical	56.1 (12.3)	55.9 (11.4)	56.3 (13.1)	56.7 (12.8)	57.5 (13.7)	56.0 (12.0)
Vitality and spirit	54.4 (15.0)	55.3 (15.4)	53.4 (14.7)	54.0 (14.3)	54.0 (14.9)	54.1 (13.9)
Emotion	78.5 (13.1)	78.9 (13.7)	78.1 (12.6)	80.5 (11.5)	81.0 (12.8)	80.0 (10.3)
Overall	63.0 (11.2)	63.4 (11.4)	62.6 (11.1)	63.7 (10.2)	64.1 (11.1)	63.4 (9.4)
SF-36						
PCS	40.4 (8.2)	39.9 (7.7)	40.9 (8.7)	39.7 (9.2)	40.2 (9.7)	39.3 (8.8)
MCS	45.0 (11.4)	45.0 (12.0)	45.0 (10.9)	46.6 (10.3)	47.6 (11.7)	45.7 (8.8)
PF	87.2 (12.6)	88.4 (11.2)	86.0 (13.9)	85.6 (14.2)	85.0 (14.3)	86.1(14.1)
RP	38.0 (35.1)	34.6 (33.3)	41.4 (36.7)	40.5 (36.5)	43.3 (35.3)	38.0 (37.5)
BP	58.0 (21.4)	57.1 (22.3)	58.8 (20.6)	56.8 (22.2)	58.7 (23.3)	55.1 (21.3)
GH	48.2 (19.2)	44.9 (19.6)†	51.6 (18.3)	50.6 (19.4)	53.6 (19.1) †	47.9 (19.4)
VT	43.3 (20.4)	43.4 (20.9)	43.3 (20.0)	43.7 (21.9)	46.8 (23.7)	40.8 (19.9)
SF	75.7 (25.4)	76.1 (26.1)	75.3 (24.8)	76.6 (23.1)	76.2 (25.9)	76.9 (20.4)
RE	49.6 (41.4)	48.3 (40.1)	50.9 (42.9)	51.8 (39.5)	54.5 (39.1)	49.4 (39.9)
MH	67.2 (19.2)	67.3 (20.9)	67.0 (17.6)	70.3 (17.1)	71.9 (18.1)	68.9 (16.1)

BP, bodily pain; GH, general health; MCS, mental component summary score; MH, mental health; PCS, physical component summary score; PF, physical functioning; RE, role limitation due to emotional problems; RP, role limitation due to physical problems; SF, social functioning; VT, vitality.

*$P < 0.05$, all the continuous variables were analysed by the exact Wilcoxon rank sum test.

†$P < 0.05$, all the categorical variables were analysed by exact chi-square test.

TABLE 2 *Number of days that subjects have taken to have resolution of symptoms*

	Numbers of days from baseline to resolution													
	Wind-cold syndrome							Wind-heat syndrome						
	Mean[a]		*P* value	75th percentile		95th percentile		Mean[a]		*P* value	75th percentile		95th percentile	
	T[b]	P[c]		T	P	T	P	T	P		T	P	T	P
n	82	80		82	80	82	80	82	83		82	83	82	83
Chills	0	0	0.91	0	0	4	4	0	0	0.48	0	0	4	4
Fever	0	0	0.50	0	0	4	4	0	0	0.39	1	0	4	4
Cough	3	2	0.53	7	10	14	16.4	2	3.5	0.38	9.3	10	20	20
Headache	1	1	0.92	4	4	10	14	1	1	0.38	4	4	7	10
Hoarseness	1	2.5	0.87	4	4	10	14	2	3	0.98	7	7	14	20
Muscle ache	3	2	0.23	4	4	10	14	2	2	0.96	4	4	20	10
Running nose	1	2	0.18	4	7	10	14	2	1	0.96	4	4	14	14
Nasal obstruction	0	0	0.84	4	4	10	14	0	0	0.88	4	4	10.2	10
Itchy throat	2.5	3	0.32	7	7	14	10	3	3	0.49	7	7	14.6	20
Sore throat	1	2	0.97	4	4	10.2	10	2	3	0.48	7	7	14	14.3
Sneezing	0	1	0.22	4	4	7	8.2	1	0	0.24	1	4	4.2	7
Total	9.5	10	0.35	14	14	21	21	10	10	0.70	14	14	20	20

[a]No significant difference can be found between treatment and placebo group by the independent sample *t*-test ($P > 0.05$).
[b]T, treatment group.
[c]P, placebo group.

to recovery ($P = 0.00$). The elder the patients, the more serious was the patient at baseline or the higher the proportion of days taking Western medication, the slower the patient recovered by observing all these variables. A patient taking more Western medication is more difficult to recover. More than 57% (treatment: 57.32%, placebo: 61.35%) of patients had taken Western medication (paracetamol, anti-histamines, soothing lozenges and/or nasal decongestants). However, removal of these patients did not alter the treatment effects on the resolution of URTIs as well as the time for symptom resolution. There is no difference in the time of recovery no matter the patient was wind heat or wind cold, taking treatment or placebo. The factors affecting the time of recovery are mainly age, Western medication at baseline, daily total symptoms score at baseline and the proportion of days taking Western medication after baseline and before recovery.

Health-related quality of life scores. The baseline health-related quality of scores between the treatment and placebo groups were not statistically different except for general health in the wind-cold syndrome group (Table 1). After the adjustment for the baseline value and the use of Western medicine, Jing Fan Bai Du san significantly improved the SF-36 general health (GH) score more than placebo in the wind-cold syndrome group on Day 7 (Table 3). No statistical significant difference was found in other SF-36 or ChQOL score on Day 7 and Day 21.

Adverse effects. Eight (11%) and 9 (11.3%) of wind-cold syndrome patients treatment and placebo groups, respectively, had reported one or more adverse effects in their diaries (Table 5). Sixteen (20%) in the placebo group and 16 (20.5%) in the treatment group of the wind-heat syndrome patients reported adverse effects. No statistically significant difference was found between the treatment and placebo groups in the incidence of adverse effects. There was also no difference between the treatment and placebo group in terms of the mean number of sick leave days during the trial period.

Discussion

To our knowledge, this was the first large randomized double-blind placebo-controlled trial (RCT) on CHM formulae. Most previous studies on CHM focussed on individual herbs which is inconsistent of the TCM principles as pointed out by the WHO.[36] This study followed the WHO recommendation to use traditional Chinese medicine herbal formulae of multiple herbs guided by the TCM diagnosis. Some people doubted the application of RCT to TCM; our study showed that a double-blind RCT that integrated TCM diagnosis pattern with traditional CHM treatments[11] could worked well. The study completion rate was over 90% suggesting that there was good patient acceptance of clinical trials with TCM. In addition to our large sample size, the external validity of the results was strengthened by enrolling patients by Western

TABLE 3 *Change in symptom and health-related quality of life score of study subjects on Day 7 post-intervention*

	Mean change (SD) in score					
	All patients		Wind-cold syndrome		Wind-heat syndrome	
	Treatment (n = 164)	Placebo (n = 163)	Treatment (n = 82)	Placebo (n = 80)	Treatment (n = 82)	Placebo (n = 83)
Symptoms						
Chills	0.7 (1.5)	0.8 (1.6)	0.7 (1.3)	1.0 (1.8)	0.8 (1.7)	0.7 (1.5)
Fever	1.1 (1.9)	0.8 (1.6)	1.1 (2.0)	0.6 (1.2)	1.2 (1.8)	0.9 (1.9)
Cough	2.5 (2.3)	2.4 (2.1)	2.7 (2.4)	2.4 (2.2)	2.2 (2.2)	2.4 (2.1)
Headache	2.1 (2.2)	2.7 (2.6)	2.1 (2.3)	2.6 (2.8)	2.2 (2.1)	2.7 (2.5)
Hoarseness	3.0 (2.4)	3.2 (2.4)	2.8 (2.5)	2.8 (2.3)	3.2 (2.3)	3.5 (2.5)
Muscle ache	3.5 (2.6)	3.2 (2.4)	3.5 (2.5)	3.3 (2.5)	3.4 (2.7)	3.2 (2.4)
Running nose	2.3 (2.5)	2.5 (2.6)	2.5 (2.5)	3.0 (2.7)	2.2 (2.4)	2.1 (2.4)
Nasal obstruction	1.9 (2.3)	1.8 (2.5)	1.9 (2.4)	1.9 (2.6)	1.9 (2.1)	1.7 (2.4)
Itchy throat	3.2 (2.4)	3.2 (2.7)	3.4 (2.5)	3.3 (2.7)	3.0 (2.2)	3.1 (2.8)
Sore throat	3.7 (2.6)	3.6 (2.7)	3.0 (2.8)	3.0 (2.8)	4.4 (2.2)	4.2 (2.6)
Sneezing	1.4 (1.9)	1.7 (2.1)	1.6 (2.1)	2.0 (2.2)	1.2 (1.8)	1.3 (1.9)
Total	2.3 (1.2)	2.4 (1.3)	2.3 (1.3)	2.4 (1.3)	2.3 (1.0)	2.3 (1.2)
SF-36 score						
PF	11.2 (12.6)	11.7 (13.2)	10.6 (11.0)	12.3 (12.7)	11.8 (14.1)	11.1 (13.7)
RP	56.4 (37.1)	53.8 (39.6)	62.2 (35.8)	49.7 (40.1)	50.6 (37.8)	57.6 (38.9)
BP	32.1 (25.8)	34.2 (25.2)	31.6 (26.7)	32.8 (26.3)	32.6 (25.1)	35.5 (24.2)
GH	20.0 (18.4)	17.7 (19.1)	23.4 (19.5)†	16.1 (15.9)†	16.5 (16.6)	19.2 (21.6)
VT	30.7 (25.2)	31.0 (23.8)	32.2 (24.4)	27.8 (24.5)	29.1 (26.0)	34.0 (22.9)
SF	19.9 (26.0)	21.1 (23.7)	20.2 (28.1)	21.0 (26.0)	19.6 (24.0)	21.2 (21.5)
RE	41.5 (43.7)	45.0 (40.4)	44.0 (43.5)	43.5 (39.4)	38.9 (44.1)	46.4 (41.5)
MH	16.4 (19.0)	14.5 (16.7)	17.0 (20.1)	12.8 (18.2)	15.9 (17.9)	16.1 (15.1)
PCS	13.3 (8.4)	13.3 (9.5)	14.0 (7.9)	12.9 (9.6)	12.7 (9.0)	13.7 (9.4)
MCS	10.8 (11.9)	10.8 (10.4)	11.4 (12.8)	9.8 (11.8)	10.2 (11.0)	11.7 (8.8)
ChQOL score						
Physical	6.7 (7.5)	7.9 (7.6)	6.4 (7.6)	8.0 (8.1)	7.0 (7.4)	7.8 (7.2)
Vitality and spirit	28.1 (18.0)	28.4 (17.6)	28.2 (19.2)	28.4 (16.9)	28.1 (16.9)	18.3 (18.3)
Emotion	–0.5 (8.0)	1.0 (6.6)	–0.5 (7.8)	0.6 (6.5)	–0.4 (8.2)	1.4 (6.8)
Overall	9.5 (6.9)	10.5 (6.9)	9.4 (6.9)	10.4 (6.5)	9.6 (6.8)	10.6 (7.3)

BP, bodily pain; GH, general health; MCS, mental component summary score; MH, mental health; PCS, physical component summary score; PF, physical functioning; RE, role limitation due to emotional problems; RP, role limitation due to physical problems; SF, social functioning; VT, vitality.
†P-value was calculated by multiple regression to compare between treatment and placebo on the changes of health-related quality of life scores, ($P < 0.05$).

TABLE 4 *Cox regression analysis of predicators of the resolution of URTIs symptoms*

Independent variables	Comparisons	Hazard ratio	P-value	95.0% CI	
				Lower	Upper
Wind cold or wind-heat (reference level: Wind-cold)	Wind-cold versus wind-heat	0.98	0.91	0.70	1.38
Treatment or placebo (reference level: Placebo)	Treatment versus placebo	1.06	0.74	0.75	1.49
Sex (reference level: male)	Male versus female	0.81	0.09	0.64	1.04
Age	Younger versus older	0.99	0.04†	0.98	1.00
Taken Western medication on Day 0 (reference level: no)	No medication versus taken WM	1.43	0.02†	1.05	1.95
Daily total symptoms score at Day 0	Lower versus higher	0.97	0.00†	0.97	0.98
Proportion of days of taking Western medication in the period from Day 0 to recovery	Lower versus higher	0.38	0.00†	0.23	0.64

†$P < 0.05$ significant in the Cox regression model.

medicine doctors to reduce the diagnostic inconsistency that might be present among patients selected by CMP.

This study could not find any significant benefit in shortening the duration or decreasing the severity of symptoms of URTIs in adult patients from the

TABLE 5 *Adverse effects reported by wind-cold syndrome patients*

	Wind-cold syndrome, *n* (%)			Wind-heat syndrome, *n* (%)	
n	Treatment 82	Placebo 80		Treatment 82	Placebo 83
Sick leave days (mean/SD)	0.15 (0.56)	0.11 (0.43)	Sick leave days (mean/SD)	0.03 (0.16)	0.03 (0.16)
Any adverse event	9 (11.25)	8 (10.96)	Any adverse event	16 (20.51)	16 (20.00)
Stomach gas	0 (0)	1 (1.37)	Stomach-ache	4 (5.13)	4 (5.00)
Diarrhoea	1 (1.25)	2 (2.74)	Thirsty	1 (1.28)	0 (0)
Insomnia	1 (1.25)	1 (1.37)	Sweating	4 (5.13)	0 (0)
Tire	1 (1.25)	1 (1.37)	Stomach gas	2 (2.56)	1 (1.25)
Stomach ache	0 (0)	1 (1.37)	Constipation	2 (2.56)	2 (2.50)
Productive phlegm	0 (0)	2 (2.74)	Vomiting	2 (2.56)	2 (2.50)
Loss of appetite	1 (1.25)	0 (0)	Insomnia	1 (1.28)	0 (0)
Constipation	1 (1.25)	0 (0)	Frequent urine	0 (0)	1 (1.25)
Sweating	1 (1.25)	0 (0)	Yellow urine	0 (0)	2 (2.50)
Thirsty	1 (1.25)	0 (0)	Productive phlegm	0 (0)	3 (3.75)
Others	2 (2.74)	0 (0)	Itchiness	0 (0)	1 (1.25)

*P value was calculated by Fisher's exact test or sign-rank test to compare the adverse event between treatment and placebo ($P > 0.05$).

treatment of Jing Fan Bai Du san for wind-cold syndrome or Ying Qiao san for wind-heat syndrome. However, Jing Fan Bai Du san was associated with a significantly greater improvement in general health than placebo in the wind-cold syndrome group.

Several other placebo-controlled trials showed a benefit from these two CHM formulae in treating URTIs when only one formula was used in selected group of patients consulting CMP.[29,30,35] It is difficult to judge the validity of the results of these trials because of some methodological flaws including problems with medication standardization, randomization, inadequacy of blinding and unclear methods. Some of these trials used traditional boiling CHM formula and additional herbs were added to individual patients that might have increased the effectiveness of the treatment,[37] which could have introduced bias and made blinding impossible. A more recently published RCT with better methodological quality did not find any difference between Yin Qiao san and Western medicine in resolving URTI symptoms.[38]

Several reasons could explain why the effectiveness of these CHM formulae found in previous studies was not replicated in this trial. CHM is recommended to be initiated at the onset of the first symptom of a URTI to be effective, but nearly, all patients in this study had symptoms for >24 hours as usually is the case in clinical practice. We also applied a more stringent criterion for the diagnosis of URTIs while trials that showed positive results included all patients who had any subjective symptom of an URTI. The dosages of the CHM formulae used in our study were the minimum doses normally recommended by over-the-counter preparations but TCM practitioners may use a higher dosage. Further studies with larger dosages should be done.

The significant improvement in the SF-36 general health score from the treatment of Jing Fan Bai Du san was interesting. This CHM formula might be able to improve the general well-being, although it could not alleviate the specific URTI symptoms, which is one of the objectives of TCM. This suggested that health-related quality of life is an important outcome measure of the effectiveness of TCM.

Both formulae were generally well tolerated with no serious adverse event being reported by patients. A high percentage of wind-heat syndrome patients reported adverse effects, but the events were mild and there was no difference between the treatment and placebo groups. Some of the reported adverse effects could be symptoms of URTIs or side effects of the concomitant Western medicine.

An unexpected finding was a negative correlation between the time of recovery and the proportion of days of taking Western medicine. It may be due to confounding in that people with more severe illness or weaker body constitutions tended to take more Western medication and recover more slowly, but the possibility of whether certain medication might slow recovery needs further investigation.

Limitations

This study had a few limitations. Only two TCM herbal formulae were tested in this study, the results could not be generalized to other TCM herbal formulae for the treatment of URTI. The formulation and dosage of the herbs in the formulae used in this study were standardized, which might not fully reflect the normal practice of TCM practitioners who often alter the formula by removing or adding specific herbs according to the patient's body constitution. However, the results would be applicable to the common situation when patients self-medicate

over-the-counter preparations of these two Chinese herbal formulae.

Anhydrous concentrated granules were used in this study, although the quality and dosage of the herbs were assured by the manufacturer to be up to the GMP standard, it cannot be certain that it had the same effectiveness as the traditional broth made from raw herbs.

Conclusions

In conclusion, Jing Fan Bai Du san might be able to improve general health more than placebo for patients with wind-cold syndrome. Patients should be advised that URTIs usually resolve after 10 days with or without any drug treatment, and these CHM formulas probably did not make any difference to the outcome of the illness. Double-blind randomized placebo-controlled trials should be used to establish objective scientific evidence on the effectiveness and side effects of TCM.

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