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Chinese herbal medicine in the treatment of acute upper respiratory tract infection: a randomised, double blind, placebo-controlled clinical trial

Key Messages

1. Neither the duration nor severity of symptoms of upper respiratory tract infection was reduced after Traditional Chinese medicine treatment with either *Jing Fan Bai Du san* or *Ying Qiao san*.
2. For patients with wind-cold syndrome, *Jing Fan Bai Du san* might be able to improve general health more than placebo.
3. Both *Jing Fan Bai Du san* and *Ying Qiao san* were well tolerated, with no excess in the incidence of side effects compared to placebo.
4. Randomised double-blind placebo-controlled trials are objective methodology to determine the effectiveness and side effects of Chinese herbal medicines.

Introduction

Acute upper respiratory tract infection (URTI) is the most common type of illness leading to consultation in primary care.[1] There is no established cure for this ailment in western medicine. In Hong Kong, Chinese herbal medicine is commonly used for treating URTI, but research on its effectiveness or side effects is meagre.

The aim of this study was to determine whether treatment with *Jing Fan Bai Du san* and *Ying Qiao san* based on traditional Chinese medicine (TCM) diagnoses would significantly enhance the resolution (reduce the duration and/or severity of symptoms) and improve quality of life in patients with URTIs in primary care.

Methods and subjects

This prospective randomised double-blind placebo-controlled trial was conducted from January 2006 to January 2007. It entailed 327 patients diagnosed with URTI in two government outpatient clinics in Hong Kong. Eligible patients were diagnosed by a registered Chinese medicine practitioner based on TCM and classified into wind-cold syndrome (n=162) and wind-heat syndrome (n=165). Patients in each group were randomised to receive concentrated TCM granules (*Jing Fan Bai Du san* for wind-cold syndrome and *Ying Qiao san* for wind-heat syndrome) or placebo for as long as the URTI symptoms persisted but up to a maximum of 10 days.

Patients recorded their symptoms and possible side effects in a diary for 21 days, and were also followed up by telephone on days 0, 1, 4, 10, 14 and 20. On day 7, patients were assessed by the Chinese medicine practitioner for the URTI symptoms, side effects, and health-related quality of life (HRQOL) measured by the SF-36 health survey and Chinese Quality of Life (ChQoL) instrument. The diary and unused TCM were returned after 21 days, using a pre-paid postal envelope. Randomisation and follow-up rates of the subjects are shown in Fig 1. The drop out rate was low, ranging from 3% to 9%.

The TCM and placebo groups were similar in terms of age, sex and other socio-demographics (Table 1), as were the mean numbers of URTI contracted in previous year and the smoking history. The baseline HRQOL scores of TCM and placebo groups were not significantly different, except for general health scores of wind-cold syndrome group (44.86 vs 53.58).

Outcome measures and data analysis

The primary outcome measure was the proportion of patients with resolution of all URTI symptoms on days 4 and 7. Each symptom was scored 0 (if absent) or 1 (if present). Secondary outcome measures included the number of days to symptom resolution, change in total symptom score, the area under the curve of the total symptoms score, change in the SF36 and ChQoL scores,

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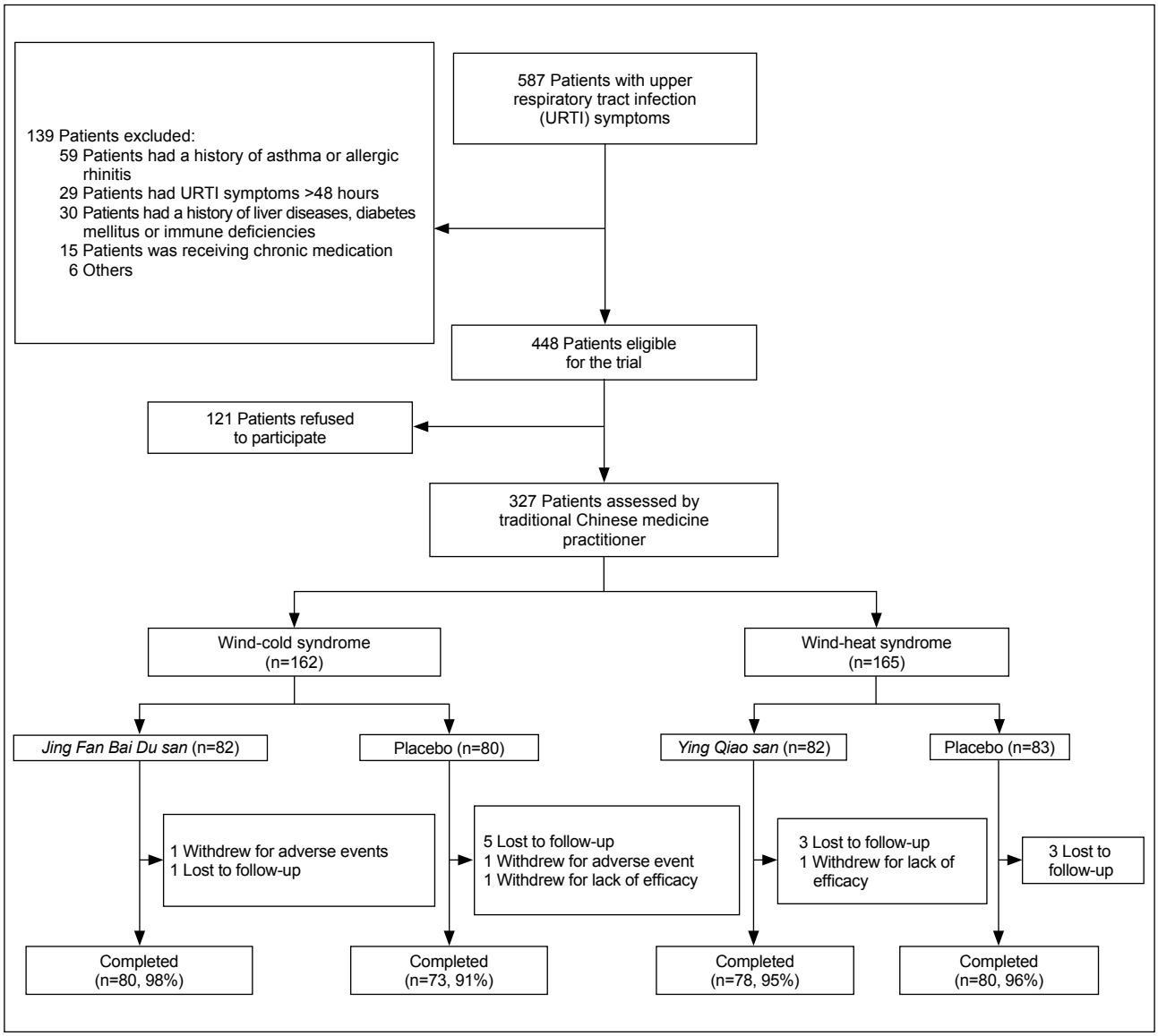

Fig 1. Patient randomisation and follow-up flow chart

number of sick-leave days, and the incidence of adverse effects. The difference in the proportion of patients with resolution of all URTI symptoms was tested separately in the wind-cold and wind-heat syndrome subgroups using Fisher's exact test. The difference in proportion on day 7 between the TCM and placebo groups was compared using logistic regression with adjustment for the use of western medicine. Sensitivity analyses were also performed. The area under the curve of the total symptom score over the 21 days between the TCM and placebo groups were compared using regression analysis with and without adjustment for the use of western medicine. The change in individual and total symptom scores over time was compared between the two groups by the sign-rank tests. The incidence of side effects in the two groups were compared by Fisher's exact test. All analyses were performed based on an intention-to-treat basis. Missing values were replaced by the last observed value.

Results

Symptoms resolution

The proportion of patients with symptom resolution was not significantly different between the TCM and placebo groups on days 1, 4, 7, 10, 14, 20 and 21, after adjusting for baseline values (Table 2). Around 50% of patients had symptoms resolved by day 7. More than 40% of patients had taken western medications (paracetamol, anti-histamines, soothing lozenges, and/or nasal decongestants), but the duration or severity of symptoms was not changed. No significant difference was found in the area under the curve of the total or individual symptom score in both the wind-cold and wind-heat syndrome subgroups (Figs 2 and 3).

Change in symptoms and health-related quality of life scores

There was no difference in the change in total or individual

Table 1. Baseline characteristics, symptoms, and health-related quality of life scores of patients

Parameters	All patients		Wind-cold syndrome		Wind-heat syndrome	
	Traditional Chinese medicine	Placebo	*Jing Fan Bai Du san*	Placebo	*Ying Qiao san*	Placebo
No. of patients	164	163	82	80	82	83
Mean±SD (range) age (years)	44.34±11.02 (20-77)	43.20±11.48 (18-74)	44.41±11.67 (22-77)	42.04±11.46 (20-73)	44.27±10.40 (20-71)	44.33±11.45 (18-74)
Female:male (%)	49:51	54:46	51:49	56:44	46:54	52:48
Mean (SD) symptom score						
Total	26.90 (13.14)	27.29 (13.60)	26.63 (14.49)	27.14 (14.06)	27.18 (11.71)	27.43 (13.26)
Chills	0.76 (1.52)	0.83 (1.57)	0.72 (1.32)	0.96 (1.78)	0.81 (1.70)	0.71 (1.34)
Fever	1.17 (1.99)	0.82 (1.59)	1.04 (2.02)	0.65 (1.20)	1.31 (1.97)	0.97 (1.87)
Cough	2.74 (2.34)	2.71 (2.12)	2.91 (2.54)	2.58 (2.08)	2.58 (2.13)	2.82 (2.16)
Headache	2.31 (2.27)	2.81 (2.52)	2.23 (2.39)	2.73 (2.59)	2.38 (2.17)	2.87 (2.48)
Hoarseness	3.12 (2.45)	3.27 (2.41)	2.94 (2.56)	2.92 (2.27)	3.31 (2.33)	3.59 (2.50)
Muscle-ache	3.67 (2.64)	3.40 (2.50)	3.79 (2.55)	3.52 (2.56)	3.55 (2.73)	3.29 (2.47)
Running nose	2.50 (2.53)	2.66 (2.51)	2.63 (2.57)	3.18 (2.63)	2.37 (2.49)	2.19 (2.31)
Nasal obstruction	2.03 (2.30)	1.90 (2.39)	2.01 (2.42)	2.03 (2.54)	2.05 (2.19)	1.78 (2.25)
Itchy throat	3.34 (2.42)	3.35 (2.70)	3.59 (2.50)	3.39 (2.64)	3.09 (2.32)	3.30 (2.77)
Sore throat	3.76 (2.61)	3.76 (2.69)	3.09 (2.84)	3.01 (2.73)	4.42 (2.19)	4.43 (2.49)
Sneezing	1.49 (1.97)	1.79 (2.04)	1.68 (2.07)	2.17 (2.18)	1.31 (1.85)	1.46 (1.85)
Mean (SD) SF-36 health-related quality of life score*						
PCS	40.37 (8.18)	39.73 (9.23)	39.88 (7.69)	40.20 (9.73)	40.86 (8.66)	39.31 (8.79)
MCS	45.01 (11.41)	46.57 (10.26)	44.97 (11.97)	47.57 (11.66)	45.05 (10.90)	45.67 (8.80)
PF	87.21 (12.64)	85.60 (14.20)	88.40 (11.21)	85.00 (14.34)	86.03 (13.90)	86.14 (14.14)
RP	37.98 (35.07)	40.50 (36.48)	34.62 (33.28)	43.31 (35.34)	41.35 (36.67)	37.97 (37.52)
BP	57.97 (21.41)	56.84 (22.24)	57.10 (22.26)	58.73 (23.26)	58.83 (20.64)	55.14 (21.28)
GH	48.23 (19.20)	50.59 (19.40)	44.86 (19.58)†	53.58 (19.13)†	51.60 (18.32)	47.90 (19.37)
VT	43.33 (20.39)	43.67 (21.93)	43.40 (20.94)	46.83 (23.73)	43.27 (19.95)	40.82 (19.91)
SF	75.72 (25.37)	76.58 (23.09)	76.12 (26.13)	76.23 (25.89)	75.32 (24.75)	76.90 (20.42)
RE	49.57 (41.39)	51.78 (39.49)	48.29 (40.07)	54.46 (39.13)	50.85 (42.88)	49.37 (39.89)
MH	67.18 (19.22)	70.29 (17.12)	67.33 (20.85)	71.89 (18.13)	67.03 (17.57)	68.86 (16.14)
Mean (SD) Chinese quality of life score						
Physical	56.10 (12.27)	56.66 (12.85)	55.94 (11.44)	57.45 (13.74)	56.26 (13.13)	55.95 (12.02)
Vitality and spirit	54.36 (15.04)	54.03 (14.33)	55.30 (15.41)	53.96 (14.87)	53.41 (14.71)	54.09 (13.92)
Emotion	78.51 (13.14)	80.47 (11.52)	78.89 (13.72)	80.96 (12.84)	78.13 (12.61)	80.03 (10.25)
Overall	62.99 (11.21)	63.72 (10.22)	63.38 (11.39)	64.13 (11.10)	62.60 (11.09)	63.36 (9.41)

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

† P<0.05 by Monte Carlo exact test for likelihood-ratio Chi-square

Table 2. Proportion of patients with resolution of symptoms

Day	Wind-cold syndrome					Wind-heat syndrome				
	Jing Fan Bai Du san (n=82)	Placebo (n=80)	P value*	Risk difference	95% CI	*Ying Qiao san* (n=82)	Placebo (n=83)	P value*	Risk difference	95% CI
1	8.5%	6.3%	0.77	0.02	-0.06-0.10	3.7%	7.2%	0.50	-0.04	-0.11-0.03
4	35.4%	40.3%	0.62	-0.05	-0.50-0.10	26.6%	36.1%	0.24	-0.10	-0.24-0.05
7	51.2%	56.0%	0.63	-0.05	-0.20-0.11	49.4%	51.3%	0.87	-0.02	-0.17-0.14
10	67.9%	70.3%	0.86	-0.02	-0.17-0.12	67.9%	70.0%	0.86	-0.02	-0.17-0.12
14	82.5%	81.1%	0.84	0.01	-0.14-0.11	73.4%	82.5%	0.19	-0.09	-0.04-0.22
20	92.5%	83.8%	0.13	0.09	-0.19-0.02	89.7%	90.0%	1.00	0.00	-0.09-0.10
21	91.3%	91.8%	1.00	-0.01	-0.08-0.09	87.2%	83.8%	0.65	0.03	-0.14-0.08

* By Fisher's exact test

symptom score between TCM and placebo groups at day 4, 7 or 21. After the adjustment for baseline values and western medicine use, patients receiving *Jing Fan Bai Du san* (in the wind-cold syndrome subgroup) had significantly greater improvement in the SF-36 general health scores at day 7 than those receiving placebo (Table 3). No statistical significant difference was found in SF-36 or ChQoL scores.

Adverse effects

One or more adverse effects were reported by 11% (placebo) and 11.25% (*Jing Fan Bai Du san*) patients in the wind-cold syndrome subgroup, and 20% (placebo) and 20.5% (*Ying Qiao san*) patients in the wind-heat syndrome subgroup. No significant difference was noted between the TCM and placebo groups in the incidence of adverse effects and the number of sick-leave days.

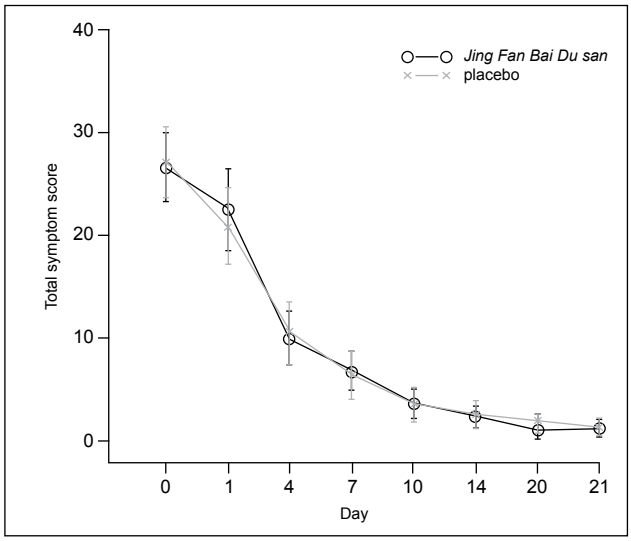

Fig 2. Comparison of total symptom scores in patients with wind-cold syndrome receiving *Jing Fan Bai Du san* or placebo

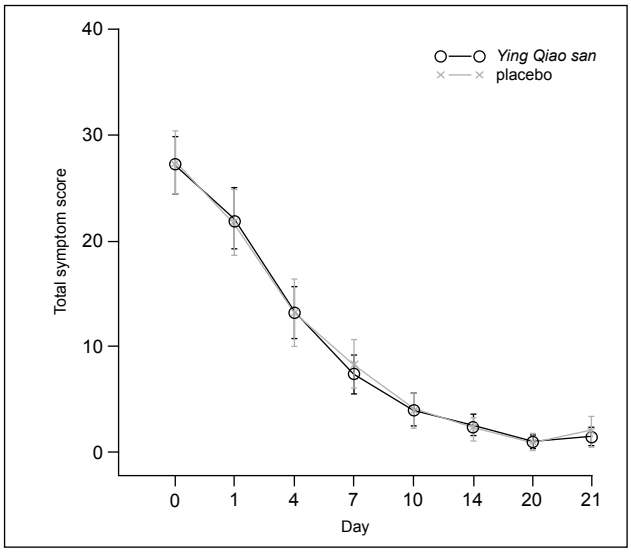

Fig 3. Comparison of total symptom scores in patients with wind-heat syndrome receiving *Ying Qiao san* or placebo

Table 3. Change in symptom and quality of life scores of patients on day 7

Parameters	All patients		Wind-cold syndrome		Wind-heat syndrome	
	Traditional Chinese medicine	Placebo	*Jing Fan Bai Du san*	Placebo	*Ying Qiao san*	Placebo
No. of patients	164	163	82	80	82	83
Mean (SD) change in symptom score						
Total	2.32 (1.15)	2.35 (1.28)	2.30 (1.28)	2.36 (1.34)	2.34 (1.01)	2.34 (1.23)
Chills	0.73 (1.49)	0.82 (1.61)	0.68 (1.28)	0.96 (1.77)	0.79 (1.68)	0.69 (1.45)
Fever	1.13 (1.92)	0.78 (1.58)	1.05 (2.01)	0.63 (1.18)	1.22 (1.84)	0.91 (1.86)
Cough	2.49 (2.31)	2.41 (2.14)	2.74 (2.42)	2.38 (2.17)	2.24 (2.17)	2.43 (2.12)
Headache	2.13 (2.20)	2.67 (2.61)	2.09 (2.31)	2.63 (2.76)	2.18 (2.09)	2.71 (2.47)
Hoarseness	3.01 (2.43)	3.15 (2.42)	2.80 (2.54)	2.81 (2.31)	3.22 (2.31)	3.46 (2.48)
Muscle-ache	3.46 (2.56)	3.24 (2.44)	3.50 (2.48)	3.32 (2.45)	3.41 (2.66)	3.16 (2.44)
Running nose	2.32 (2.47)	2.52 (2.57)	2.46 (2.54)	3.01 (2.68)	2.17 (2.39)	2.08 (2.39)
Nasal obstruction	1.92 (2.27)	1.79 (2.45)	1.91 (2.41)	1.89 (2.56)	1.94 (2.13)	1.70 (2.36)
Itchy throat	3.18 (2.36)	3.20 (2.71)	3.41 (2.46)	3.32 (2.65)	2.95 (2.24)	3.09 (2.79)
Sore throat	3.68 (2.58)	3.58 (2.72)	3.01 (2.79)	2.95 (2.77)	4.37 (2.17)	4.16 (2.55)
Sneezing	1.43 (1.93)	1.67 (2.05)	1.61 (2.05)	2.04 (2.20)	1.24 (1.78)	1.33 (1.85)
Mean (SD) change in SF-36 health-related quality of life score*						
PCS	13.32 (8.44)	13.30 (9.45)	13.95 (7.85)	12.87 (9.57)	12.70 (8.99)	13.69 (9.39)
MCS	10.77 (11.91)	10.80 (10.35)	11.35 (12.77)	9.83 (11.80)	10.19 (11.04)	11.68 (8.81)
PF	11.19 (12.63)	11.69 (13.18)	10.58 (10.96)	12.29 (12.70)	11.79 (14.14)	11.14 (13.66)
RP	56.41 (37.12)	53.81 (39.55)	62.18 (35.75)	49.65 (40.13)	50.64 (37.79)	57.59 (38.89)
BP	32.11 (25.82)	34.23 (25.17)	31.60 (26.68)	32.79 (26.30)	32.62 (25.09)	35.53 (24.20)
GH	19.96 (18.39)	17.72 (19.10)	23.42 (19.53)†	16.08 (15.87)†	16.50 (16.60)	19.20 (21.63)
VT	30.67 (25.16)	31.03 (23.78)	32.24 (24.36)	27.78 (24.46)	29.10 (26.01)	33.99 (22.89)
SF	19.87 (26.02)	21.11 (23.68)	20.19 (28.08)	21.01 (26.02)	19.55 (23.97)	21.20 (21.50)
RE	41.45 (43.73)	45.03 (40.41)	44.02 (43.48)	43.52 (39.42)	38.89 (44.11)	46.41 (41.49)
MH	16.41 (19.01)	14.49 (16.65)	16.97 (20.14)	12.78 (18.17)	15.85 (17.93)	16.05 (15.07)
Mean (SD) change in Chinese quality of life score						
Physical	6.69 (7.45)	7.88 (7.61)	6.43 (7.57)	7.98 (8.07)	6.96 (7.36)	7.79 (7.20)
Vitality and spirit	28.13 (18.04)	28.35 (17.56)	28.18 (19.20)	28.39 (16.87)	28.07 (16.93)	18.32 (18.27)
Emotion	-0.45 (7.96)	0.97 (6.63)	-0.53 (7.75)	0.56 (6.45)	-0.37 (8.22)	1.35 (6.81)
Overall	9.49 (6.85)	10.52 (6.88)	9.38 (6.94)	10.40 (6.49)	9.60 (6.80)	10.63 (7.26)

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

† P<0.05 by sign-rank test

Discussion

This study adhered to guidelines of the consolidated standards for reporting trials. The numbers of patients in each subgroup were similar. Double-blind clinical trials based on TCM diagnoses were feasible. Over 90% of the

patients completed their treatment courses, suggesting good acceptance to clinical trials with TCM.

This study did not reveal any significant benefit in terms of reducing the duration or severity of URTI symptoms after the treatment of *Jing Fan Bai Du san* (for wind-cold syndrome) or *Ying Qiao san* (for wind-heat syndrome). Other placebo-controlled trials have shown a benefit from these two TCMs in treating URTI.[2-4] However, it is difficult to judge the validity of these trials because of methodological flaws such as problems with medication standardisation, randomisation, blinding, and analytic methods. A recently published randomised controlled trial also did not find any difference between *Yin Qiao san* and western medicine in resolving URTI symptoms.[5]

Jing Fan Bai Du san was associated with a significantly greater improvement in general health than placebo in the wind-cold syndrome subgroup. It might be able to improve general well-being although it could not alleviate specific URTI symptoms. An important objective of TCM is to improve the general well-being. This suggests that HRQOL might be an important outcome measure for TCM-treated patients.

Both TCM formulae were well tolerated with no serious adverse event reported by the patients. Although a higher percentage of wind-heat syndrome patients reported adverse effects, the events were mild and no different from those encountered on placebo treatment. Some of these adverse events might have been related to the URTI itself or to the western medicine use.

Several factors could have affected the effectiveness of TCM. The TCM should be initiated at the onset of URTI symptoms, but most patients had already endured symptoms for more than 24 hours. We applied a more stringent criterion for the diagnosis of URTI, compared to trials that showed positive results included all patients with any subjective symptoms. The TCM formulae were given as minimum doses. Further studies with larger dosages should be performed.

Conclusions

No effect on URTI symptom resolution or reduction was demonstrated after treatment with *Jing Fan Bai Du san* or *Ying Qiao san*. Nonetheless, in patients with wind-cold syndrome. *Jing Fan Bai Du san* might be able to improve general health more than placebo. Both TCM formulae were well tolerated, and there was no difference in the incidence of side effects compared to placebo.

Randomised double-blind placebo-controlled trials can be used to determine the effectiveness and side effects of TCM treatments. It is the recommended research methodology to obtain objective evidence on the usefulness of TCM treatments.

Acknowledgements

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