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Chinese herbs in treatment of influenza: A randomized, double-blind, placebo-controlled trial

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Summary
Objective: To investigate the efficacy and safety of Antiwei, a traditional Chinese prescription, in the treatment of influenza.
Methods: In a multi-center, randomized, double-blind, placebo-controlled trial, we recruited 480 adults aged 18 to 65 years within 36 h of onset of influenza-like symptoms. There were 225 patients with confirmed influenza. Eligible patients were randomly assigned 6 g of Antiwei (n = 360) or placebo (n = 120) twice daily for three days. All patients recorded their temperature and symptoms on diary cards during treatment. Analyses were performed in both the influenza-like population and the influenza-confirmed population.

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Introduction

Influenza caused by infection with either influenza A or B viruses, is one of the most common and important respiratory illnesses affecting all ages. Uncomplicated influenza is generally resolved over 2- to 5-day period, although cough and malaise can persist for weeks. Influenza epidemics such as the influenza A (H1N1) pandemic in 2009, which is the first pandemic since 1968, are associated with increased morbidity and hospitalization rates, and excess mortality within the most vulnerable populations, including the elderly, infants and those with underlying medical conditions.

Although drugs such as the adamantanes (i.e., amantadine and rimantadine) and the neuraminidase inhibitors (i.e., oseltamivir and zanamivir) are available to treat or prevent influenza, recent emergence of adamantane resistant strains has rendered these agents less effective. In addition, sporadic cases of oseltamivir-resistant influenza A (H1N1) virus infection have been reported worldwide following the H1N1 pandemic of 2009. Even though vaccination strategies against influenza A (H1N1) virus are now present in China, some patients may look beyond conventional treatments and consider complementary and alternative medicines, including traditional Chinese medicine (TCM), in this situation. TCM represents one aspect of Chinese medical philosophy that is characterized by an emphasis on maintaining and restoring balance. Chinese medicinal herbs, the most important component of TCM, are derived from plants and usually incorporate one or more herbs as the basic drugs to treat the disease. Supplemental use of Chinese medicinal herbs were found to be beneficial in the management of severe acute respiratory syndrome (SARS) in 2003 and, based on that supplementary treatment, Chinese medicinal herbs might also show promise for treating or preventing influenza and influenza-like illness. Some randomized controlled trials (RCTs) have been published, but the evidence for treating or preventing influenza by TCM has not yet been convincingly established, due to poor reporting quality and small sample size.

Antiwei granule is a traditional Chinese prescription, consisting of Mahuang (Herba Ephedra), Baimaogeng (Rhizoma Imperatae), Gegen (Radix puerariae), Guizhi (Ramu-lus Cinnamomum), Kuxingren (Semen Armeniacae Amarum.), Ganjiang (Rhizoma Zingiberis) and Gancao (Radix Glycyrrhizae). One gram of Antiwei granule equals 3.83 g of crude drug. The resource, pharmacological actions and components in this formula are listed in Table 1. According to TCM, Mahuang and Baimaogeng in this formula, which are regarded as “the principal” herbs, could relieve exterior disorder and defervesce. Gegen and Guizhi, which serve as “the Minister”, cooperate with “the principal” to relieve exterior syndrome and defervesce. Kuxingren and Ganjiang are “the adjuvant drug”, which can open the inhibited lung-energy, regulate the flow of Qi, eliminate phlegm and relieve cough. Gancao serves as “the guiding drug”, which can moisten lung to arrest cough and coordinate all of the drug actions of this formula.

Antiwei has been used widely based on clinical experience rather than evidence of RCTs in the treatment of influenza-like illness (such as fever, headache, pain and cough) in China. Therefore, a prospective, multi-center, randomized, double-blind, placebo-controlled clinical trial was undertaken to investigate the efficacy and safety of Antiwei granule for the treatment of naturally acquired influenza in humans.

Subjects and methods

Patients and ethics

Eligible patients, who presented with fever over 37.4 °C and at least one respiratory symptom (cough, sore throat, or nasal symptom) and at least one constitutional symptom (headache, fatigue, myalgia, thirst or chills), were recruited from emergency departments from January to June, 2007. The inclusion criteria were as follows: (1) clinical diagnosis of influenza; (2) age 18 to 65 years; (3) within 36 h of onset of influenza-like illness; (4) written informed consent. The exclusion criteria were as follows: (1) any treatments after onset of influenza-like illness; (2) other confirmed upper respiratory viral infections; (3) suspected bacterial infection (based on symptoms, leukocyte count > 10.0 × 109/L or neutrophil granulocyte ≥ 80%); (4) pregnancy or breast-feeding; (5) allergies to food additives, drugs, and any components in Antiwei granule; (6) current alcoholism or drug abuse; (7) severe diseases of cardiac, respiratory, hepatic, renal, central nervous system, hematopoietic system cancer; (8) the inability to understand and complete this study; (9) current psychiatric illness or dementia; (10) clinically important chronic illnesses or known HIV infection, receiving steroids or other immuno-suppressants, or having been vaccinated against influenza in the previous 12 months. We also required that patients of childbearing age use contraception.

Results: Antiwei increased patients’ recovery by 17% (P < 0.001), and reduced the severity of illness measured by the median symptom score by 50% (P < 0.001) in both the influenza-like and the influenza-confirmed populations, compared to placebo. The influenza-confirmed patients reported reductions in the severity of fever (P = 0.002), cough (P = 0.023) and expectoration (P = 0.004) after one-day of treatment with Antiwei, compared to placebo. The adverse event profiles were similar for Antiwei and placebo.

Conclusion: Antiwei was effective and well tolerated in treatment of natural influenza infection in adults. Antiwei represents a clinically valuable intervention in the management of influenza.
| Chinese name | Pharmaceutical name | Source | Pharmacological actions in traditional Chinese medicine | Weights (%) |
|-------------|----------------------|--------|--------------------------------------------------------|-------------|
| Mahuang     | Herba Ephdra         | The dried herbaceous stem of *Ephedra sinica* Stapf, *Ephedra equisetina* Bunge or *ephedra intermedia* Schrenk et C.A. Meyer (family Ephedraceae) | To induce seating for releasing the superficials in cases of wind-cold affliction; to relieve asthma; to induce diuresis for relieving edema caused by wind | 10.99       |
| Bai mao gen | Rhizoma Imperatae    | the dried rhizome of *Imperata cylindrica* Beauv. Var. major (nees) C.E. Hubb. (family Gramineae) | To cool blood, arrest bleeding, clear heat and induce diuresis for the treatment of epistaxis and hematuria due to blood heat, edema, jaundice, and stranguria associated with heat | 32.68       |
| Gegen       | Radix puerariae      | The dried root of *Pueraria lobata* (Wild) Ohwi or *Pueraria thomsonii* Benth. (family Leguminosae) | To reduce heat in cases of exterior syndrome with fever and painful stiffness of the back and nape; to relieve thirst in febrile diseases and diabetes mellitus; to arrest diarrhea in spleen insufficiency; to promote eruption for measles | 16.48       |
| Guizhi      | Ramulus Cinnamomum   | The died Young stem of *Cinnamomum cassia* Presl. (family Lauraceae) | To induce sweating for releasing the muscles in cases of wind-cold affliction; to warm and unblock the meridians to relieve various pains due to cold and congealing blood; to stimulate menstrual discharge for treating amenorrhea | 10.99       |
| Ganjiang    | Rhizoma Zingiberis   | The dried rhizome of *Zingiber officinale* (Wild.) Rose. (family Zingiberaceae) | To warm the spleen and stomach for the relief of nausea, vomiting, abdominal pain and diarrhea due to deficiency-cold of the spleen and stomach; to warm the lung for treating chronic cough with thin, white and foamy expectoration | 6.59        |
| Ku xing ren | Semen Armeniacae Amarum. | The dried ripe seed or kernel of *Prunus armeniaca* L. var *ansu* Maxim., *Prunus Sibirica* L., *Prunus mandshurica* (Maxim.) Koehne or *Prunus armeniaca* L. (family Rosaceae) | To relieve cough and dyspnea with profuse expectoration; to relieve constipation | 10.99       |
| Gancao      | Radix Glycyrrhizae   | The dried root and rhizome of *Glycyrrhiza uralensis* Fisch., *Glycyrrhiza inflata* Bat. or *Glycyrrhiza glabra* L. (family Leguminosae) | To replenish qi and tonify the heat for treating arrhythmia in cases of heart qi deficiency; to tonify the spleen for treating lassitude, anorexia and loose bowels in cases of spleen insufficiency; to relieve epigastric colic and spastic pain of the limbs; to dispel phlegm and arrest cough; to clear heat and counteract toxin for treating sore throat, boils, sores and drug overdose; most frequently for modulating the ingredients in a prescription | 10.99       |

Data from Classified dictionary of traditional Chinese medicine by Zhu-fan Xie.13
The Medical Ethics Committee of West China Hospital at Sichuan University approved this study (No. IRB-2007-13), and it is in accordance with the recent principles of the Declaration of Helsinki. All patients gave informed consent and were free to withdraw from the study at any time.

Study design and interventions
This was a prospective, multiple-center, randomized, double-blind, placebo-controlled trial, which was undertaken at eight Chinese centers: three in North China, three in Northeast China, one in Northwest China, and one in West China. Patients were randomized in a double-blind fashion to receive either Antiwei granule or placebo. The randomization code was generated by the PRCO PLAN of the analysis system of SAS (Version 6.12 for Windows). Allocation details were sealed in an envelope, and were unknown both to investigators and participants in this study.

Antiwei and placebo were supplied by Tasly Group (Tianjin, China), the herbal composition of Antiwei is presented in Table 1. The placebo granule was composed of starch and bitter agents, but was visually indistinguishable from the Antiwei in appearance, color, size and packaging. The subjects in the Antiwei group received 6 g of Antiwei granule twice a day for three days, whereas the patients in the placebo group received 6 g of placebo twice a day for three days. All patients were treated in an equivalent fashion. We assessed compliance by daily diary cards and review of the returned medication at the end of treatment.

Assessments
We took present, past and personal medical histories, measured vital signs such as temperature, respiration rate, heart rate and blood pressure, did physical examinations of pharynx, larynx and lung in respiratory system, and collected baseline virological samples before treatment. After accepting treatment, patients recorded their axillary’s temperature every 2 h for up to 12 h on day one. On days 2 and 3, they recorded their axillary’s temperature at 8am, 10am, 12am, 4pm and 8pm in a diary card. To exclude other respiratory illnesses, subjects received chest X-ray screening before beginning treatment. The presence and severity of influenza symptoms, including cough, sore throat, nasal obstruction and rhinorrhea, headache, fatigue, myalgia, thirst and chills, were recorded once daily using a four-point scale (0 absent, 1 mild, 2 moderate, and 3 severe). The first record was performed when the patient was admitted, and the next two records (on days 1 and 3 after treatment) were done in the morning. Influenza was confirmed by a direct immunofluorescent antibody assay (DFA) of nasopharyngeal swabs, which showed sensitivities of 89.7% for influenza A virus and 87.9% for influenza B virus and specificities of 99.3% for influenza A virus and 100% for influenza B virus. Treatment assignment was blinded during virological testing, which was done at West China Hospital, Sichuan University, Chengdu.

The primary endpoints were severity of illness (measured by the mean symptom scores for the whole treatment period) and the number of recovered patients in the intention-to-treat and influenza-confirmed populations. Recovery was defined as absence of fever (temperature < 37.4 °C) and all nine symptoms (chills, headache and myalgia, nasal obstruction, sore throat, fatigue, cough, rhinorrhea, expectoration, and thirst). Secondary outcomes included the length of time to alleviate fever within the first 24 h after treatment, the severity of each symptom, and the rate of influenza-virus-positive conversion to negative for the influenza-confirmed population at entry.

Adverse effects record
Participants were required to record any unexpected signs, symptoms, or feelings during the treatment period, and routine tests of blood, urine, stool, as well as hepatic and renal functions and electrocardiogram (ECG) were performed at admission and again after treatment to assess safety in both groups.

Statistical analysis
A sample size of 135 for the Antiwei group and 45 for the placebo group, at a ratio of 3:1, were calculated according to published data to have a power of 80% or greater to detect a difference of 10 percent in recovery rate, assuming a significance level of 0.05. Sample size calculations were performed using a normal approximation to the Wilcoxon rank-sum test.

Influenza-like and influenza-confirmed populations were both analyzed, with the influenza-like population consisting of randomized patients who received at least one dose of medication in this study. Safety analyses were performed on those populations, which included all patients who received at least one dose of medication and who had at least one follow-up for safety, whether or not they were withdrawn prematurely.

All analyses were performed using Stata 11.0. Measurement data showing a normalized distribution were described as mean ± standard deviation and analyzed with analysis of variance to determine the difference between the Antiwei and placebo group. Measurement data showing a non-normalized distribution were described as median and analyzed by the Wilcoxon rank-sum test. Frequency data were analyzed using the chi-squared ($\chi^2$) or Fisher’s tests. The primary endpoints were analyzed using the survival method. Kaplan–Meier curves were constructed and significance-tested using the log-rank method. For the mean symptom scores we used analysis of variance. The rate of influenza-virus-positive conversion to negative was compared between different groups with $\chi^2$ test. $P \leq 0.05$ for two-tailed tests was considered to be significant.

Results

Trial profile and patient characteristics
A total of 480 eligible patients were enrolled and randomly assigned to receive Antiwei granule ($n = 360$) or placebo ($n = 120$). Of these, 34 patients withdrew from the study early for several reasons including lost to follow-up (Antiwei: $n = 6$; Placebo: $n = 7$), protocol violation (Antiwei: $n = 15$; Placebo: $n = 3$), and refusal to continue (Antiwei: $n = 1$; Placebo: $n = 2$). Overall, 225 (48.2%) patients had laboratory-confirmed influenza (Fig. 1). Of these, 125...
(55.6%) had influenza A, 74 (32.9%) had influenza B and 26 (11.5%) had both influenza A and B (Table 2). All available data from these patients were included in the efficacy and safety analyses. No differences were observed between two groups in the demographics and clinical characteristics. Safety of the study drug was assessed for all 480 patients.

**Efficacy**

For influenza-confirmed patients, Antiwei resulted in significantly more patients recovering or showing a reduction in the severity of illness. The number of patients recovering after three days of treatment was 42 of 177 (23.2%) in the Antiwei group \((P = 0.009)\) (Fig. 2) compared to 3 of 48 (6.25%) in the placebo group, and this benefit was also seen in the patients with influenza-like disease (86/353 vs. 10/114, \(P < 0.001\)). Similarly, Antiwei resulted in significant reductions in the total symptom score after three days of treatment in the influenza-confirmed population (15.2 ± 6.25 vs. 10.26 ± 7.72, \(P < 0.001\)) and in the influenza-like population (−15.07 ± 6.32 vs. −8.81 ± 6.99, \(P < 0.001\)) compared to placebo.

After one-day treatment, the improved percentage of symptom score (difference between the symptom scores at baseline and after one-day treatment is divided by the symptom score at baseline) in fever (57.9% vs. 34.4%, \(P = 0.002\)), headache and myalgia (96.6% vs. 95.8%, \(P = 0.871\)), nasal obstruction (26.1% vs. 36.9%, \(P = 0.892\)), rhinorrhea (34.5% vs. 23.4%, \(P = 0.107\)), sore throat (25.7% vs. 17.0%, \(P = 0.088\)), fatigue (24.8% vs. 25.9%, \(P = 0.863\)) or thirst (35.3% vs. 21.5%, \(P = 0.072\)) (Fig. 3). At the same time, the median temperature fell by 0.8 °C from baseline in the Antiwei group but by only 0.4 °C in the placebo group (\(P = 0.0001\)). Treatment benefit for fever was apparent as...
Figure 3  Improved percentage in symptom scores after one-day treatment in influenza-confirmed patients. *P < 0.05, Placebo vs. Antiwei. Improved percentage in symptom scores defines that difference between the symptom score at baseline and after one-day treatment is divided by the symptom score at baseline.

Figure 4  Time to alleviation of fever in influenza-confirmed patients within the first 24 h after treatment. P < 0.05 Placebo vs. Antiwei.

Figure 5  The number of influenza-virus-positive patients in influenza-confirmed population after three-day treatment.
A variety of Chinese herbs have been widely used as antipyretic drugs for clearing accumulated heat in the lungs, according to the theory of TCM. One recent study by Kubo T. et al. showed that there is a more antipyretic effect of Mao-to, a Japanese herbal medicine, for treatment of type A influenza infection in children, in comparison to Oseltamivir.\(^{29}\) The Japanese traditional herbal medicine includes Mahuang, Guizhi, Kuxingren and Gancao, which as components were included in Antiwei. In our study, the antipyretic effect was apparent within 24 h of Antiwei administration, when influenza symptoms are generally most troublesome. Although we did not assess economic effects, the indirect costs of influenza such as workplace absenteeism and performance at work could be improved according to the clinical benefits observed in the influenza-confirmed population and in the population with influenza-like illness.\(^{30}\)

Studies in animal experiments and in vitro, have confirmed that Antiwei can inhibit growth of a variety of virus, including influenza A and B, respiratory syncytial virus (RSV), adenovirus etc (data not shown). We now show that Antiwei can significantly reduced the positive rate of influenza virus after treatment. These findings are consistent with results from studies of other antiviral drugs for influenza and other self-limiting viral diseases, for which increased therapeutic benefit is obtained when treatment is started as early as possible after symptom onset.\(^{31}\)

The duration of cough and expectoration was shorter and the severity of the two symptoms was generally lower in the Antiwei groups (data not shown). Influenza is transmitted by virus-laden secretions. Cough and expectoration could be the most distressing symptoms of influenza and also contributes to the spread of infection. Patients who received Antiwei had significantly lower positive rate of virus on laryngopharynx swabs than those in the placebo group. Such differences, together with improvement of symptoms, including cough and expectoration, may help to reduce transmission of the virus.

Antiwei was generally well tolerated, with almost no adverse events reported. Only one patient given Antiwei reported mild paroxysmal palpitation, which was resolved within two days without additional treatment. This symptom was not associated with discontinuation rates in the Antiwei group compared to placebo. No other adverse effects or abnormalities in laboratory test were associated with Antiwei treatment. It must be noted that the Antiwei contains Mahuang, which has been reported to have some side effects (such as chest pain, hypertension, arrhythmia, myocardial infarction, stroke, or death)\(^ {32}\) when served as a dietary supplement for weight reduction and performance enhancement, but the use of Mahuang in this study was not associated with any significant adverse events. In our prescription, 6 g of Antiwei equals to 23 g of crude herbs, in which there is 2.5 g of Mahuang, so the daily dose of Mahuang was only 5.0 g, which is a small dosage compared with the conventional dose in other TCM treatments.

We recognize that this study does have some potential limitations. We did not include follow-up after treatment, and the symptoms of influenza were observed for only 4 days, thus by the end of study many patients had not fully recovered. Therefore, the duration of illness and the time of alleviation could not be exactly evaluated. In addition, the protocol specifically excluded individuals with medical conditions which would place them in high-risk populations that are often associated with more severe influenza.

In conclusion, our study clearly indicated that Antiwei was an effective treatment of influenza-conformed and influenza-like illness in otherwise healthy adults, and Antiwei can provide an alternative to conventional treatment for influenza or influenza-like symptoms. Antiwei might also be a potent medication for use in influenza pandemics and in situations where a shortage of antiviral agents and vaccines exists. Our findings provide a rationale for continuing studies of this agent in the treatment of influenza, and these should now include studies in children and in high-risk populations. Further large-scale studies to investigate the other antiviral effect of Antiwei, and studies of its mechanism(s) are also now required.

**Conflict of interest statement**

None declared.

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