Mixture prepared with Chinese medicines in terms of releasing exterior cold and clearing interior heat: its efficacy and safety in patients with seasonal influenza - a randomized controlled trial

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Abstract

OBJECTIVE: To assess the efficacy and safety in 105 patients with seasonal Influenza in Beijing, the mixture prepared with Chinese medicines follows the treatment regimen of releasing exterior cold and clearing interior heat.

METHODS: Total 330 patients with seasonal influenza were enrolled and randomly and averagely divided into the Chinese herbal medicine, the western medicine and the Chinese patent medicine group. They were treated with Chinese medicine Oseltamivir Phosphate Capsules and the Scattering Wind and Resolving Toxins Capsules. The main efficacy indicators were the antifebrile onset time and recovery time of body temperature. The efficacy and safety of the mixture was scientifically evaluated. Comparisons of several variables were analyzed.

RESULTS: Median antifebrile onset time of the Chinese herbal medicine group was significantly shorter than the western medicine group (P < 0.05) and the Chinese patent medicine group (P < 0.05). The median antifebrile recovery time of the Chinese herbal medicine group was significantly shorter than the Chinese patent medicine group (P < 0.05). The groups evaluated by TCM symptom pattern effect, both the Chinese herbal medicine group and Western Medicine group were better than the Chinese patent medicine group (P < 0.05). The disappearance rate of main symptoms and some minor symptom patterns of the Chinese herbal medicine group were higher than the other 2 groups.

CONCLUSION: The mixture of releasing exterior cold and clearing interior heat could significantly shorten the fever time with safety.

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Keywords: Releasing exterior cold and clearing interior heat; Influenza; efficacy; Mixture prepared with Chinese medicines

INTRODUCTION

Influenza is an acute viral respiratory disease caused by the influenza virus. Children, the elderly and the low immunity people that suffer from influenza are often accompanied by complications, some even dies. Thus, the effective prevention and treatment of influenza has become one of the major public health problems we are facing. Professor Zhou Ping-an, the famous veteran TCM doctor, Dongfang Hospital’s Chief Expert and famous respiratory therapist concluded that the basic pathogenesis of influenza in northern China is cold in the exterior, heat in the interior, heat and toxin canopied from his clinical experiences. With the method of releasing exterior cold and clearing interior heat and venting toxin from interior, Professor Zhou formulated the mixture of releasing exterior cold and clearing interior heat. To show the efficacy of the mixture, the western medicine group was set for the Oseltamivir Phosphate Capsules had the anti-viral effect, the Chinese patent medicine group was set for the scattering wind and resolving toxins capsules could scatter wind and resolve toxin. The report of the using of this medicine on 105 seasonal influenza patients in Beijing is as follows.

METHODS AND MATERIALS

Diagnostic criteria

Western diagnostic criteria for influenza: reference to the Ministry of Health, ‘Guidelines for the Diagnosis and Treatment of Influenza (2011 edition)’

Traditional Chinese medicine diagnostic criteria referred to ‘New TCM drug Clinical Research Guidelines’

(a) Aversion to cold with fever, even shivering, nasal congestion, severe headache and body pain, red face and pharyngeal, cough, etc. (b) Rapid pulse, normal or red tongue, white or yellow thin coating. (c) Acute, similar symptom patterns, rapid spread, epidemic.

Traditional Chinese Medicine (TCM) symptom pattern identification criteria referred to ‘Internal Chinese Medicine’ exterior cold and interior heat, common cold.

Main symptoms: (a) fever; (b) aversion to cold with fever; (c) headache; (d) body pain; (e) pharyngeal pain. minor symptoms: (a) nasal congestion; (b) runny nose; (c) cough; (d) cough with sputum; (e) thirst; (f) nausea; (g) vomiting; (h) diarrhea; (i) lack of strength; (j) vexation and agitation.

Tongue manifestation: yellow thin or greasy coating. Pulse manifestation: floating or soggy pulse.

The main symptoms are essential; meanwhile the patient should have more than 3 minor symptoms. Furthermore, it should be diagnosed combining tongue and pulse manifestation.

Inclusion criteria

The inclusion criteria were as follows: (a) the patient with influenza during influenza season, was in line with above criteria. (b) The patient was in line with TCM syndrome of exterior cold and interior heat. (c) the patients should be in the course of the disease within 48 hours, axillary temperature ≥ 38.0 °C; (d) the patient’s age was between 18 to 65; (e) patient was volunteered in subjects and signed informed consent; (f) patients did not participate in other clinical research in 3 months; (g) patients had ability to comply with the study throughout.

Exclusion criteria

Patients were excluded if they had any of the followings: (a) The patient had taken antiviral drugs or traditional Chinese medicine to treat the common cold before the first time came to the outpatient department; (b) Blood WBC was greater than the upper limit of normal; (c) Chest X-ray examination with inflammatory exudate; (d) Combined with cardiovascular, liver, kidney and hematopoietic system and other serious primary disease, immunodeficiency disease, cancer, mental illness, no self-knowledge, liver and kidney function abnormalities (liver function 1.5 times higher than normal). (e) Pregnancy, breast-feeding women, allergies. (f) Those who did not meet the inclusion criteria that were mistakenly included; (g) Those that met the inclusion criteria, but did not use the test drug after enrollment; (h) The case without any record could be rejected after treatment.

Shedding criteria

(a) Self-exiting during the test; (b) serious adverse events and complications and special physiological changes happened; (c) other various reasons such as the patient withdraw before trial ended or the lost and death.

Materials

This research was based on National Science and Technology Support Program and approved by the Institutional Review Board of Dongfang Hospital Affiliated to Beijing University of Chinese Medicine. These 330 influenza patients were recruited at the outpatient department of Dongfang Hospital Affiliated to Beijing University of Traditional Chinese Medicine from November 2014 to March 2016. According to the random number table of Excel 2003, the patients were randomly divided into the groups of the Chinese herbal medicine group (the mixture of releasing exterior cold and clearing interior heat), the Western Medicine group (Oseltamivir Phosphate capsules) and the Chinese patent medicine group (Scattering wind and resolving toxins capsules). Every group has 110 patients.
The envelopes were used for randomization concealment, the surfaces of them was numbered 1-330 and the allocation was sealed in them. When the patients were included, the envelope was unsealed according to order of the number. The patients were put into the group according to the allocation, it would not be changed. At last, there were 47 males and 63 females in the Chinese herbal medicine group, age (36.3 ± 12.7); course (25.3 ± 12.1) h, body temperature (38.5 ± 0.5) °C; 52 males and 58 females were in the western medicine group, age (36.6 ± 12.6), course (21.8 ± 11.5) h, body temperature (38.5 ± 0.4) °C; 54 males and 56 females were in the Chinese patent medicine group, age (34.2 ± 12.4), course (22.6 ± 13.2) h, body temperature (38.4 ± 0.4) °C. There were no significant differences in the general materials among the three groups (P > 0.05).

Methods
Treatments: the Chinese herbal medicine group was treated with the mixture to release exterior cold and clear interior heat (Radix Bupleuri 10 g, Radix Scutellariae 10 g, Radix Herba Ephedrae 5 g, Semen Armeniacae Amarum 9 g, Gypsum Fibrosum 30 g, Radix et Rhizoma Glycyrrhizae 5 g, Flos Lonicerae Japonicae 15 g, Radix Isatidis 10 g) (specification: 100 mL per bag, provided by Dongfang Hospital) Therapeutic dosage: The first 1-3 d with 3 bags per day, 4th to 5th day with 2 bags per day; the Western Medicine group was treated with Oseltamivir Phosphate capsules (specification: 75 mg per capsule, E Hoffmann-La Roche Ltd.) Therapeutic dosage: 75 mg per time, 2 times a day; the Chinese patent medicine group was treated with Scattering Wind and Resolving Toxins capsules (specification: 0.52 mg per capsule, Anhui Jiren Pharmaceutical CO., Ltd.), Therapeutic dosage: 2.08 mg per time, 3 times a day. The treatment lasted 5 d.

If the patient’s body temperature was greater than 38.5 °C and sustained more than 4 h or the body temperature was greater than 39 °C during the treatment, the patient could be treated with paracetamol. There was no other medicine involved for treating influenza.

Observation indicators
The antifebrile onset time and recovery time of body temperature: body temperature is measured by the axillary temperature. The antifebrile onset time of the body temperature was calculated from the beginning of medication to the temperature decreased by 0.5 °C; recovery time calculated from the beginning of medication to body temperature dropped to 37.0 °C, and did not raise to higher than 37.0 °C again.

Efficacy based on TCM syndrome: the efficacy on TCM syndrome in 3 groups was compared with N-molipine law on the 3rd and 5th day after using the medicines. Efficacy index = (points before treatment-points after treatment) / points before treatment × 100%.

RESULTS
Comparison of the rejected and shedding cases in each group
A total of 330 influenza patients were recruited. 3 were rejected from western medicine group, 1 was a herpes zoster patient misdiagnosed. Another 2 were rejected because of not taking medicine. 5 were shed in the Chinese herbal medicine group. 1 due to violation of the plan and 4 due to loss of follow-up; 4 were shed in Western Medicine group. 1 case due to diarrhea, 1 case due to violation of the plan and 2 cases due to loss of follow-up; 10 were shed in the Chinese patent medi-

Statistical analysis
SPSS 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY, USA) was used for data processing. Basic statistical description Qualitative data used the frequency table, percentage or constituent ratio. The mean ± standard deviation ( x ± s) of quantitative data would be selected, if it showed normal distribution. The median (M) (quartile spacing (QR = Q75-Q25)) would be selected if it showed non-normal distribution. To compare the differences among 3 groups, the chi-square test was used for the Enumeration data; the paired t-test would be used for metrological data if the data showed normal distribution, if not, the Kruskal-Wallis rank sum test (ANOVA) would be used. Non-normal data were analyzed by Nemenyi test. P < 0.05 was statistically significant level.
Chinese group. 1 case was due to skin rash, 2 was due to violation of the plan, and 7 was due to loss of follow-up. The remained 308 patients had good compliance and there was no significant difference of the patients in the 3 groups (P = 0.199) (Figure 1).

Comparison of antifebrile onset time and recovery time in each group
Table 1 shows the median antifebrile onset time of the Chinese herbal medicine group was 1.5 h, shorter than the Western Medicine group (P = 0.02) and the Chinese patent medicine group (P = 0.01), but the difference was not statistically significant between the Western Medicine group and the Chinese patent medicine group (P = 0.94). The difference among the onset time of the three groups was statistically significant (P = 0.002), the Chinese herbal medicine group was superior to the Western Medicine group and the Chinese patent medicine group.

Table 2 shows the median antifebrile recovery time of the Chinese herbal medicine group is 47 h, significantly shorter than the Chinese patent medicine group which of that is 66 h (P < 0.01). But the difference was not statistically significant between the Western Medicine group and the Chinese patent medicine group (P = 0.94). The difference among the recovery time of the three groups was statistically significant (P < 0.01). Chinese herbal medicine group and Western Medicine group were superior to Chinese patent medicine group.

Comparison of TCM symptom patterns before and after the treatment in each group
As can be seen from Table 3, after 3 days’ treatment, statistical significance of TCM syndrome was found between the Chinese herbal medicine group and the Chinese patent medicine group (P < 0.05). Meanwhile, statistical significance was also found between the western medicine group and the Chinese patent medicine group (P = 0.03). But there was no statistical significance between Western Medicine group and the Chinese herbal medicine group (P = 0.15). After 5 days’ treatment, there was significant difference between the Chinese herbal medicine group and the Western Medicine group (P = 0.02). Also, there was significant difference between the Chinese herbal medicine group and

Figure 1 The flowchart of study
The incidence of complications
After the treatment of 330 patients, 2 of pneumonia occurred respectively in the Western Medicine group and the Chinese patent medicine group, the 4 were followed up, the symptoms were improved after anti-in-
Influenza is a term used in both Western Medicine and TCM. As a category of externally-contracted febrile disease in TCM, its incidence is closely related to regions and climate. The different characteristics of climate in north and south of China plays an important role in the occurrence of influenza, and thus affect the pathogenesis and the using of the drug to prevent the disease. In northern China, the influenza is the most common disease in winter and spring. It is highly contagious and has a wide epidemic range. In northern China, the indoor temperature is high, and the outdoor temperature is low during winter and spring, so the Chinese herbal medicine group was treated with the Chinese medicines with the dosage: First 4th bags per day, 3 bags per day with 3 days; the Western Medicine group was treated with Osehmativir Phosphate capsules (specification: 75 mg per capsule, F. Hoffmann-La Roche Ltd.). Therapeutic dosage: 2.08 mg per time, 3 times a day. After 3 and 5 days’ treatment, there was no significant difference in the disappearance rate of minor symptoms. Minor symptom disappearance rate = minor symptom disappearance cases / the minor symptom occurred on the day of the enrollment × 100%.

### Table 4 Comparison of symptoms disappearance rates before and after the treatment in each group [n(%)]

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Time</th>
<th>Fever</th>
<th>Aversion to cold with fever</th>
<th>Headache</th>
<th>Body pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chinese herbal medicine</td>
<td>105</td>
<td>The 3rd day</td>
<td>86/105 (81.9)</td>
<td>70/93 (75.3)</td>
<td>51/90 (56.7)</td>
<td>44/90 (48.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The 5th day</td>
<td>105/105 (100)</td>
<td>91/93 (97.8)</td>
<td>85/90 (94.4)</td>
<td>84/90 (93.3)</td>
</tr>
<tr>
<td>Western Medicine</td>
<td>103</td>
<td>The 3rd day</td>
<td>78/103 (75.7)</td>
<td>59/95 (62.1)</td>
<td>44/90 (48.4)</td>
<td>45/90 (50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The 5th day</td>
<td>99/103 (96.1)</td>
<td>92/95 (96.8)</td>
<td>73/91 (80.2)</td>
<td>81/90 (90)</td>
</tr>
<tr>
<td>Chinese patent medicine</td>
<td>100</td>
<td>The 3rd day</td>
<td>58/100 (58)</td>
<td>51/91 (56.0)</td>
<td>47/94 (50)</td>
<td>71/92 (71.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The 5th day</td>
<td>95/100 (95)</td>
<td>82/91 (90.1)</td>
<td>77/94 (81.9)</td>
<td>71/92 (71.2)</td>
</tr>
</tbody>
</table>

### Table 5 Comparison of minor symptom disappearance rates before and after the treatment in each group [n(%)]

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Time</th>
<th>Nasal congestion (%)</th>
<th>Runny nose (%)</th>
<th>Pharyngeal pain (%)</th>
<th>Thirst (%)</th>
<th>Cough (%)</th>
<th>Cough with Sputum (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chinese herbal medicine</td>
<td>105</td>
<td>The 3rd day</td>
<td>28/76 (36.8)</td>
<td>(31.6)</td>
<td>(34.1)</td>
<td>(30.3)</td>
<td>27/89 (31.6)</td>
<td>19/92 (21.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The 5th day</td>
<td>56/76 (73.7)</td>
<td>(72.2)</td>
<td>(58.8)</td>
<td>(77.5)</td>
<td>32/92 (43.4)</td>
<td>37/71 (51.2)</td>
</tr>
<tr>
<td>Western Medicine</td>
<td>103</td>
<td>The 3rd day</td>
<td>22/84 (26.2)</td>
<td>(25.2)</td>
<td>(34.1)</td>
<td>(26.2)</td>
<td>43/80 (57.3)</td>
<td>36/97 (46.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The 5th day</td>
<td>55/84 (65.5)</td>
<td>(54.9)</td>
<td>(58.5)</td>
<td>(53.7)</td>
<td>34/89 (40.4)</td>
<td>19/92 (21.6)</td>
</tr>
<tr>
<td>Chinese patent medicine</td>
<td>100</td>
<td>The 3rd day</td>
<td>13/79 (16.5)</td>
<td>(15.9)</td>
<td>(27.7)</td>
<td>(28.2)</td>
<td>22/78 (29.7)</td>
<td>9/87 (11.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The 5th day</td>
<td>46/79 (58.2)</td>
<td>(60.9)</td>
<td>(62.6)</td>
<td>(51.3)</td>
<td>40/78 (53.1)</td>
<td>21/87 (28.1)</td>
</tr>
</tbody>
</table>

Notes: the Chinese herbal medicine group was treated with the Chinese medicines with the dosage: First 1-3 days with 3 bags per day, 4th to 5th day with 2 bags per day; the Western Medicine group was treated with Osehmativir Phosphate capsules (specification: 75 mg per capsule, F. Hoffmann-La Roche Ltd.). Therapeutic dosage: 75 mg per time, 2 times a day; the Chinese patent medicine group was treated with scattering wind and resolving toxins capsules. Therapeutic dosage: 2.08 mg per time, 3 times a day. After 3 days and 5 days’ treatment, there was no significant difference in the disappearance rate of minor symptoms in the three groups (P > 0.05). Symptom disappearance rate = symptom disappearance cases / the symptom occurred on the day of the enrollment × 100%.

### Safety indicators

There was 1 case of diarrhea in the western medicine group, the symptoms were mild, after stopping the medicine, the symptoms were improved; there was 1 case of rash in the Chinese patent medicine group, symptoms disappeared after stopping the medicine; there were no significant adverse reactions in the remaining patients. There was no statistically significant difference in safety among the three groups (P > 0.05).

### DISCUSSION

Influenza is a term used in both Western Medicine and TCM. As a category of externally-contracted febrile disease in TCM, its incidence is closely related to regions and climate. The different characteristics of climate in north and south of China plays an important role in the occurrence of influenza, and thus affect the pathogenesis and the using of the drug to prevent the disease. In northern China, the influenza is the most common disease in winter and spring. It is highly contagious and has a wide epidemic range. In northern China, the indoor temperature is high, and the outdoor temperature is low during winter and spring, so patients are easily affected by the inner heat and external cold. The patients can have the symptoms of both sides. The clinical manifestations are aversion to cold, fever, headache, body pain, fatigue etc. Also, it is accompanied with the symptoms of pharyngeal pain run-
ny nose, tears, cough and other respiratory symptoms. Few subjects accompanied with loss of appetite, abdominal pain, bloating, vomiting and diarrhea and other gastrointestinal symptoms. We believe that at the beginning of the influenza the epidemic toxin comes inward and transmits pathogenic heat that causes pharyngeal pain, thirst with a desire to drink, cough with yellow sputum etc. If the epidemic toxin reversely transmits to the pericardium, it will cause unconsciousness and delirious speech. Therefore, the pathomechanism of influenza in northern China in the winter is external cold and internal heat and disease involving both the exterior and interior.

Based on above, according to the pathomechanism and his more than 50 years’ clinical experience, Professor Zhou Ping-an treated it with the mixture of releasing exterior cold and clearing interior heat with the method of release the exterior and dissipate cold, clear interior heat. The mixture is modified with based upon the formulas like Minor Bupleurum Decoction, Ephedra, Apricot Kernel, Gypsum and Licorice Decoction and Lonicera and Forsythia Powder. The former clinical trial showed Ephedra, Apricot Kernel, Gypsum and Licorice Decoction plus Lonicera and Forsythia Powder could be used as an alternative treatment of H1N1 influenza virus infection.⁶ Radix Bupleuri, Radix Scutellariae can clear and discharge damp-heat from the Shaoyang level and regulate the pivot of shaoyang; Radix Herba Ephedrae, Semen Armeniacae Amarum, Gypsum Fibrosum, Radix et Rhizoma Glycyrrhizae can release exterior and clearing interior; Flos Lonicerae Japonicae, Radix Iatidis can vent heat.

From pharmacology study, the Radix Bupleuri and Radix Scutellariae has the function of anti-inflammation regulating immune and anti-virus.⁷—¹⁰ Zhao found that Semen Armeniacae Amarum, Gypsum Fibrosum and Radix et Rhizoma Glycyrrhizae can regulate the T-cell subpopulation in mice exposed to influenza virus A.¹¹ Flos Lonicerae Japonicae has the effects of broad-spectrum anti-bacteria and antivirus, also, the components have anti-inflammatory, antipyretic, and antiendotoxin functions.¹² Also, the component of Radix Iatidis contains the polysaccharide, it has the anti-IAV activity against human seasonal influenza viruses (H1N1 and H3N2) and avian influenza viruses (H6N2 and H9N2) in vitro.¹³

This research was based on professor Zhou Ping-an’s treating influenza with ‘releasing exterior cold and clearing interior heat method’. The research team set up 2 control groups of Oseltamivir Phosphate Capsules (Tamiflu) and scattering wind and resolving toxins capsules. To show the efficacy and anti-viral effect of the mixture to release exterior cold and clear interior heat, the Tamiflu group was set. To show the efficacy of the releasing exterior cold and clearing interior heat method was better than the only use of scattering wind and resolving toxin method, so we set up the scattering wind and resolving toxin group, even though, the scattering wind and resolving toxin capsules was not an internationally recognized medicine to treat the influenza. But the vivo experimental study showed this medicine had the effect of preventing and treating H1N1 influenza virus on mice. Meanwhile, the clinical research showed the scattering wind and resolving toxin capsules had a significant efficacy on treating the fever (wind-heat pattern) caused by viral upper respiratory infection. Also, it was a recommended Chinese patent medicine of treating mild influenza (wind-heat pattern) in ‘Guidelines for the diagnosis and treatment of influenza (2011 edition)’.¹⁴ The results showed that the median antifebrile onset time of the Chinese herbal medicine group was shorter than the Western Medicine group (\( P = 0.02 \)), but as for recovery time, the difference was not statistically significant between the Western Medicine group and the Chinese herbal medicine group (\( P = 1.0 \)). From the clinical study, neuraminidase inhibitors can effectively relieve the symptoms of influenza patients, shorten the duration and length of stay, reduce complications, and may reduce the mortality of patients, especially when it is used in the early 48 h. Oseltamivir is an oral medicine approved for the using of children (> 1-year old) and adults. This shows that Releasing the mixture has a certain anti-viral effect. In addition, taking the 3rd and 5th days’ effect of treatment into consideration, compared with Oseltamivir, the mixture has a better effort on improving TCM symptom pattern. Even though the rate of disappearance of main symptoms and minor symptoms between 2 groups was not statistically significant, but in Tables 4 and Tables 5 we can see, compared with the Western Medicine group and the Chinese patent medicine group, the Chinese herbal medicine group has a better effort in disappearance rate of symptoms to some extent. So, we can say that the treatment regimen of releasing exterior cold and clearing interior heat can improve the symptoms of influenza. The incidence rate of complications of the groups was not statistically significant, so the mixture with the potency of releasing exterior cold and clearing interior heat is safe and reliable in the treatment of seasonal influenza in Beijing.

Compared with scattering wind and resolving toxins capsules, the the mixture has obvious advantages in all aspects, which shows that the method of releasing exterior cold and clearing interior heat is more suitable than the method of only scattering wind and resolving toxins to treat the seasonal influenza in Beijing. Furthermore, it enriches the theory of pattern differentiation and treatment in TCM.

In conclusion, the mixture of releasing exterior cold and clearing interior heat has a significant effect on influenza virus, which can significantly shorten the fever time. As for improving the symptoms, it is also better
REFERENCES