Clinical Controlled Study of Integrative Chinese and Western Medicine in Treating 49 Cases of SARS*

JIAO Qiang (焦 强)[1], WANG Biao (王 飚)[1], ZHANG Rui-lin (张瑞麟)[1], WANG Bao-guo (王保国)[2], FENG Li-min (冯力民)[2], WANG Hai-jian (王海箭)[1], LUO Yan-nan (罗燕楠)[1], YAN Xiong (剡 雄)[1], SHEN Hong-qiang (沈红强)[1], MA Ying-min (马英明)[1], XIONG Yun (熊 云)[1], CHEN Wei-heng (陈卫衡)[1], MA Da (马 达)[1], CHENG Ting (程 桯)[1], and ZHOU Wei (周 卫)[1]

ABSTRACT **Objective**: To evaluate the efficacy of integrative Chinese and western medicine (ICWM) in treating severe acute respiratory syndrome (SARS) patients. **Methods**: Through parallel control design, 49 SARS patients were observed. Used as control, there were in the western medicine (WM) group 29 patients, who were treated with Ribavirin, Levofloxacin, Thymopentin, Azithromycin, methylprednisolone, etc., on the basis of "Recommended Protocol for Infectious Atypical Pneumonia" (abbreviated as "Recommended Protocol") issueed by Ministry of Health. As the treated group, there were in the ICWM 20 cases. The protocol for treatment of SARS in "Special Science and Technological Action to Prevent and Treat SARS" (abbreviated as "Special S-T Action"), issued by Ministry of Science and Technology, together with the same WM as those for the control group. **Results**: (1) Time from the disease onset to the symptom improvement were 5.10±2.83 days and 7.62±2.27 days in ICWM and WM group respectively, $P<0.05$; (2) As to corticosteroid (CS) amount and days before reducing dosage, 2 groups showed no significant difference, $P>0.05$; (3) There was no significant difference in the time from disease onset to the body temperature normalization and the total amount of CS and the duration of using CS before reducing it to 80 mg between the ICWM group and the WM group; (4) The days and amounts for use CS after reducing between the ICWM group and the WM group were significantly different ($P<0.05$). **Conclusion**: There were obvious advantages in ICWM to treat SARS, compared with that of WM alone, especially in improving the clinical symptoms, promoting the recovery of immune function, promoting the absorption of pulmonary inflammation and reducing the dosage and duration of CS treatment.

KEY WORDS severe acute respiratory syndrome, integrative Chinese and western medicine treatment, corticosteroid, clinical study

Severe acute respiratory syndrome (SARS) is an infectious respiratory illness that is caused by a previously unrecognized coronavirus in human beings. Human being has no natural immunity to the virus. This disease is a new challenge to physicians since they don't have any experience in treating SARS. From the view of traditional Chinese medicine (TCM), SARS belongs to the category of "pestilence". The ancient TCM practitioners have left behind much valuable experiences and medical works in treating pestilence. In clinical practice, significant advantages of TCM in treating SARS patients were observed. TCM won a good opportunity of development.

The SARS medical team from Beijing Wangjing Hospital, joined by a team from Beijing Tiantan Hospital, participated in "Special Science and Technological Action to Prevent and Treat SARS" ("Special S-T Action") project, which was advocated by Ministry of Science and Technology (MST). The two teams managed the patients admitted in separate clinical wards (Wangjing Hospital and Tiantan Hospital were in charge of 3rd and 6th ward) in Chaoyang Health Center for Women and

* The study is supported by The Ministry of Science and Technology of 863 Programme "The Developing the Key of Technique and Products for Preventing SARS" (No. 2003AA208101)

1. Wangjing Hospital, China Academy of Traditional Chinese Medicine, Beijing (100102); 2. Beijing Tiantan Hospital

Correspondence to: Dr. JIAO Qiang, Wangjing Hospital, China Academy of Traditional Chinese Medicine, Beijing (100102); Tel: 010-64711199 Ext. 4043; Fax: 010-64724815; E-mail: jiaoqiang@263.net

CJIM 2003;9(3) : 175—180

Children's Designated SARS Hospital from April 25 to May 31, 2003. In order to explore the effect of integrative Chinese and western medicine (ICWM) in treating SARS, this clinical prospective study compared the patients treated with western medicine (WM) alone versus those treated with ICWM in these two independent wards. This investigation conducted a preliminary assessment of the treatment effects by two different approaches on SARS.

METHODS

Patient Selection

Inclusion criteria: According to "The Clinical Diagnosis Criteria of the Infectious Atypical Pneumonia (Trial)" issued by Ministry of Health (MOH) on April 27, 2003, all patients were diagnosed as SARS and confirmed by Beijing Center for Disease Control (CDC). The patients were informed of the application of ICWM treatment regimens when admitted.

Exclusion criteria: Patients who had drug allergic diathesis; those with adverse events taking place in them after treatment; those with poor compliance, resulting in the drug administration is not performed following the medical order and those who dropped out from the study with their data lost for follow-up.

Study Design

Adopted was the prospective parallel matched control design.

General Data

Fifty-two cases diagnosed as SARS patients were allocated to two groups after admission. In the treated group (ICWM, $n=22$), 4 were males and 18 females, age ranging from 16 to 66 years, mean 39.4 years. In the control group (WM, $n=30$), 12 were males and 18 females, age ranging from 18 to 63 years with mean age of 33.3 years. According to "The Clinical Diagnosis Criteria of Severe Infectious Atypical Pneumonia" issued by MOH on April 27, 2003, the patients were further subdivided into mild grade and severe grade subgroup. There were 17 cases in mild grade and 5 cases in severe grade in the treated group. All of the patients were in mild grade in the control group. There were altogether 52 cases for assessment in the investigation. One case died from cerebral hemorrhage. Two cases were transferred to another hospital and thus lost to our study. Of these three missing cases, two were in the treated group and one in the control group. The exclusion rate was 5.8%. The remaining 49 cases all fully recovered from SARS (Table 1). There was insignificant difference between the two groups in terms of age, sex, WBC count and body temperature before treatment ($P>0.05$). The two groups were comparable.

However, there was significant difference between the two groups with regards to the grade of illness, the lymphocyte absolute value and the score of chest film before treatment ($P<0.05$). Before treatment, the grade of illness were severe and the lymphocyte absolute value were lower in the treated group than those in the control group. The score of the chest film in the treated group was higher than that in the control group ($P<0.05$). See Table 1.

Table 1. Comparison of the General Data between Two Groups before Treatment ($\bar{x}\pm s$)

Group	n	Sex		Age (year)	WBC count ($\times10^9$/L)	Lymphocyte count ($\times10^9$/L)	Body temperature (℃)	Illness degree		Score of the chest X-ray
		Male	Female					Mild	Severe	
Treated	20	4	16	38.0±11.1	5.17±4.11	0.78±0.35*	38.89±0.38	16*	4*	10.55±5.35**
Control	29	12	17	33.3±12.0	4.53±2.48	1.11±0.55	38.79±0.79	29	0	4.41±1.32

Note: * $P<0.05$, ** $P<0.01$, compared with the control group

Treatment Regimens

Control group: The patients were administered with Ribavirin (0.5—1 g, intravenously dripped, 1/d, 14—20 days as one treatment course), Levofloxacin (0.3 g, intravenouly dripped, 2/d, 14—20 days as one treatment course), Thymopentin (100 mg, intravenously dripped, 1/d, 14—20 days as one treatment course), Azithromycin (0.5 g, intravenously dripped, 1/d, 14—20 days as one treatment course), methylprednisolone (80—240 mg, intravenously dripped, 2/d, after 7—14 days half the dosage was given), based on "Recommended Protocol for Infectious Atypical Pneumonia" ("Recommended Protocol") issued by MOH.

Treated group: In addition to the general treatment in control group, we used the protocol of "Special S-T Action" issued by MST. TCM recipe No. Ⅰ was used in treating hyperpyrexia stage, its ingredients are ephedra 5 g, bitter apricot 12 g, plaster 45 g, anemarrhena rhizome 10 g, honeysuckle flower 15 g, forsythia fruit 12 g, cape jasmine fruit 12 g, baikal skullcap root 12 g, capillary wormwood herb 15 g, kudzuvine root 15 g, pseudostarwort root 15 g, and perilla leaves 10 g, decocted in water, taken orally for 3—7 days. TCM recipe No. Ⅱ was used for treating cough and asthma, its ingredients are American ginseng 15 g, lilyturf tuber 10 g, Chinese magnolia vine fruit 10 g, dogwood 12 g, pepperweed seed 15 g, tatarian aster root 15 g, loquat leaf 12 g, earthworm 12 g, red sage root 12 g, red peony root 12 g, Chinese globeflower 8 g, baikal skullcap root 10 g, and snakegourd peel 15 g, decocted in water, taken orally for 5—14 days. TCM recipe No. Ⅲ was administrated in the recovery stage, its ingredients are pseudostarwort root 15 g, lilyturf tuber 15 g, glehnia root 15 g, largehead atractylodes rhizome 15 g, loquat leaf 15 g, villous amomum fruit 6 g, charred triplet 30 g, milkvetch root 15 g, kudzuvine root 15 g, red sage root 15 g, tangerine peel 6 g, and siberian solomonseal rhizome 15 g, decocted in water, taken orally for 10—20 days. In addition, the patients of hyperpyrexia were supplemented with Zixue powder (紫雪散, 0.5 g, 2/d) or Angong Niuhuang bolus (安宫牛黄丸, 1 bolus, 2/d) or Qingkailing injection (清开灵注射液, 30 ml, intravenously dripped, 1/d). The patients who had chest distress, short of breath and severe pulmonary infiltration on chest film were treated with Danshen injection (丹参注射液, 30 ml, intravenously dripped, 1/d). The patients who had palpitation, sweating, lassitude and shortness of breath were treated with Shenmai injection (参脉注射液, 30 ml, intravenously dripped, 1/d) or the Shengmai injection (生脉注射液, 30 ml, intravenously dripped, 1/d).

Clinical Observation Criteria

Adopted were the observation forms of "Special S-T Action", issued by MST. The symptoms, the temperature and the adverse effect were recorded every day. Blood routine was examined every 2—4 days, chest film was examined every 3—5 days. The chest film was scored based on the criteria issued by MST. The amount and duration of corticosteroid (CS) usage in the course of treatment and recovery and during reducing and withdrawing of CS according to the medical order was calculated.

Observation Criteria

According to "The Discharge Criteria of Infectious Atypical Pneumonia" issued by MOH on April 27, 2003, patients would be discharged from hospital if the patients met three conditions: (1) normal temperature for no less than seven days, (2) marked improvement of the respiratory tract symptoms, and (3) obvious absorption of infiltration observed on the X-ray chest film. In clinical practice, the following clinical observation parameters were set for each patient. (1) Body temperature: Recorded was the highest temperature before treatment, and its duration from admission to the first day of the 7 consecutive days in which the body temperature kept stable at below 37℃. (2)

CJIM 2003;9(3) : 175—180

Symptoms: symptom improvement means the disappearance of aversion to cold, headache, arthralgia, myalgia and diarrhea; and the relieving of cough, chest distress, shortness of breath, palpitation and lassitude. Record the duration from admission to the beginning of all symptoms remission. (3) Blood routine: Record the lowest total WBC count and lymphocyte absolute value at the onset of illness. Record the duration from admission to the first day when the total WBC count and lymphocyte absolute value recover to normal lower limit, as well as the duration of normal count stabilization. (4) The X-ray chest film: severest score of chest film patchy shadow was recorded as the score before treatment. Record the duration from admission to the first day when the chest film got clear (seen in two consecutive films) (5) CS: Record the total amount and duration of using CS (>80 mg daily every day), as well as the amount and duration of using CS of 80 mg daily.

Statistical Analysis

All the data were re-checked and managed by computer database. SPSS 10.0 was used to conduct the statistical analysis. χ^2 test was used for enumeration data and student's t test was used for measurement data.

RESULTS

Comparison of the Duration in Body Temperature Reduction

The body temperature was normalized in all the patients of both groups. The body temperature below 37℃ was seen in all the patients 6 days after admission. There was no statistically significant difference in the duration of the body temperature recovery between the two groups ($P>0.05$, Table 2).

Comparison of the Duration in Symptom Improvement

All the complaints about aversion to cold, headache, arthralgia, myalgia and diarrhea disappeared. Cough, chest distress, shortness of breath, palpitation and lassitude were relieved. The average duration for symptom improvement was 5.10 ± 2.83 days in the treated group and 7.62 ± 2.27 days in the control group. There was statistically significant difference in duration on symptom improvement in the two groups ($P<0.05$, Table 2).

Comparison of the Duration for the Blood Routine Improvement

There was no statistically significant difference in duration in recovery of WBC count and lymphocyte absolute value ($P>0.05$). It took around 8 days for WBC count and lymphocytes absolute value to normalize after admission (Table 2).

Comparison of the Time Needed in Pulmonary Patchy Shadow of Chest Film Improvement

The patchy shadow observed on chest film all disappeared after therapy, the clearance of patchy shadow on chest film was observed around 15 days after admission. There was no statistically significant difference in the time needed for the observation of clear chest film in the two groups ($P>0.05$, Table 2).

Comparison of the Total Amount of CS before and after Reducing-withdrawing the Dosage

There was no statistically significant difference in the total amount of CS usage before reducing the dosage to under 80 mg per day in the two groups ($P>0.05$). CS use was averaged at 2658 mg/patient in the treated group, and 2130 mg in the control group (Table 2). But after reducing the dosage the total amount used was 273 mg and 496 mg respectively, the difference being significant ($P<0.05$).

Comparison of the Duration in Using CS before Reducing the Dosage

There was no statistically significant difference in the duration of using CS before reducing the daily dosage to less than 80 mg in the two groups ($P>0.05$). The duration of CS usage was averaged at 18 days/patient in the treated group, and 21 days in the

Table 2. Comparison of the Effect between Two Groups after Treatment ($\bar{x}\pm s$)

Group	n	BTNT (day)	SRT (day)	WLNT (day)	CFSDT (day)	ACBRD(mg/case)	DCBRD (day)	ACARD (mg/case)	DCARD(day)
Treated	20	5.60±2.98	5.10±2.83*	8.30±5.00	14.90±5.70	2658.00±1811.03	17.75±8.97	273.00±357.66*	17.50±14.81*
Control	29	6.03±2.10	7.62±2.27	8.00±5.88	15.69±7.40	2130.35±1256.42	21.24±6.05	495.69±162.99	29.69±8.90

Notes: * $P<0.05$, compared with the control group; BTNT means body temperature normalization time, SRT means symptom remission time, WLNT means WBC and lymphocyte normalization time, CFSDT means chest film shadow disappearance time, AVBRD means amount of used corticoid before reducing dosage, DCBRD means duration of using corticoid before reducing dosage, ACARD means amount of used corticoid after reducing dosage, DCARD means duration of using corticoid after reducing dosage

control group (Table 2).

DISCUSSION

Reducing and Stabilizing the Body Temperature

In treatment of high fever, it took around 6 days for temperature to normalize in the two groups. According to clinical experience in the past, CS plays an important role in cryogenic treatment due to its inhibitory feature in anti-inflammation and anti-immunologic reaction. Together with CS, heat-clearing and detoxifying herbal medication in TCM also acts to reduce the temperature gradually. The patients in treated group did not have recurrence of fever. But there were 4 patients in control group who had recurrence of fever, making it difficult for physicians to reduce CS. From the view of TCM, when epidemic toxin invaded, stagnation of evil heat in Fei was the syndrome differentiation in early stage of SARS. The application of TCM recipe No. Ⅰ aims to clear away heat and toxic agents, dispell exogenic wind and facilitate the flow of the Fei-qi. Modified Maxing Shigan decoction (麻杏石甘汤) was the major recipe to reduce the temperature steadily and gradually. It facilitates the reducing of CS medication with no worry about recurrence of fever.

Clinical Symptoms Improvement

With respect of improving clinical symptoms, it took two days less to achieve the symptoms improvement in treated group than the control group. Knowing the remission of clinical symptoms, the patients improved their quality of life and raised their confidence in overcoming SARS. From the view of the TCM, the patients had cough, chest distress, shortness of breath, stagnation of evil heat in Fei and impaired ventilation. The downflowing of the Fei qi was the syndrome differentiation, and the treating principle should be cough-dyspnea suppression and heat-clearing blood-activating. The symptoms were relieved obviously by TCM recipe No. Ⅱ and Danshen injection. In the recovery stage of SARS, the patients had palpitation, lassitude, thirsty, sweating, and dyspnea. Qi and yin deficiency was the syndrome differentiation, and therefore they were treated with reinforcing-qi and nourishing-yin, activating Pi and harmonizing Wei. Apparent improvement was achieved by treating patients with TCM recipe No. Ⅲ and Shengmai injection or Shenmai injection. The efficacy was satisfactory.

Promoting Lymphocytes Recovery

It took around 8 days for WBC count and lymphocyte absolute value to get normalized in the two groups after hospitalization. Owing to the fact that the lymphocyte absolute value in treated group were lower than that of control group before treatment, we failed to see statistically significant difference in the duration of the recovery of WBC count and lymphocyte absolute value. However, the ranges of lymphocyte absolute value before and after treatment was greater in treated group than that in the control group. Therefore, it suggested that the ICWM therapy has played a role in promoting the immune function recovery. We further observed that the recovery tendency of blood routine is: The lymphocyte steadily elevated, the total WBC count usually sur-

CJIM 2003;9(3) : 175—180

passed the upper limit of normal value, and reached (10.5—26.0)×10^9/L, and later on gradually normalized again. We hold that the cause of increase in WBC count was possibly due to the application of CS.

Promoting the Absorbing of Chest Film Patchy Shadow

The disappearance of patchy shadow in the chest X-ray film was one of the features that marked the cure of SARS. It took around 15 days to achieve the disappearance of the patchy shadow in the chest film in the two groups after hospitalization. Because the scores of the chest film in treated group was higher than that in the control group before treatment, we can say that the pulmonary infiltration was severer in the treated group than that in the control group. After treatment, there was no statistically significant difference in the time needed for disappearance of patchy shadow in the two groups. The amplitude of absorption of the patchy shadows in the X-ray chest film in the treated group was greater than that in the control group. Therefore, ICWM therapy had promoted the absorption of pulmonary inflammation. Activating blood circulation to remove stasis in TCM was efficient in promoting the absorption of pulmonary inflammatory lesion. The early application of Danshen injection had a beneficial effect in promoting the absorption of chest film patchy shadow.

Reducing the Dosage and Duration of CS Usage

In the course of clinical treatment, applying TCM created favorable conditions for reducing CS usage as soon as possible. Although there was no statistically significant difference in the duration in using it before reducing the daily dose to less than 80 mg in the two groups, the duration of CS use was averaged at 18 days in the treated group for every patient and 21 days in the control group. If the comparison was made with median number in the treated group was 17 days and in the control group was 25 days. There was significant difference in the time needed for CS use between the two groups. In short, the course of the CS use in the treated group was shorter than that in the control group. As to the course of withdrawing CS, there was significant difference between two groups in terms of the total amount of CS use and the duration of usage. Therefore, the use of CS in the treated group was less than that in the control group. Consequently, the adverse effects of CS was reduced obviously.

Chaoyang Health Center for Women and Children's Designated SARS Hospital was a newly founded specific hospital, its medical equipment has not been completed yet, thus some parameters could not be checked such as lymphocyte subset profile determination, a very significant parameter etc. There were involved in the study mainly mild cases, with only 4 severe patients, therefore in choosing observation parameters, blood oxygen saturation was not used as an observation parameter, because in the majority of patients before and after treatment the blood oxygen saturation was in the range of normal values.

This clinical control study showed that in treating SARS, particularly in the respect of improving clinical symptoms, elevating quality of life, promoting immune function recovery, promoting absorption of pulmonary inflammation, reducing the dosage of CS and shortening the therapeutic course, ICWM had obvious superiority compared with using WM treatment alone. Hence we should further deepen TCM clinical study, and ICWM approach in treating SARS should be actively popularized.

(Received June 26, 2003)