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The Use of an Herbal Formula by Hospital Care Workers During the Severe Acute Respiratory Syndrome Epidemic in Hong Kong to Prevent Severe Acute Respiratory Syndrome Transmission, Relieve Influenza-Related Symptoms, and Improve Quality of Life: A Prospective Cohort Study

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ABSTRACT

Objectives: To investigate the efficacy of an herbal formula in the prevention of severe acute respiratory syndrome (SARS) transmission among health care workers. The secondary objectives are to investigate quality of life (QOL) and symptomology changes among supplement users, and to evaluate the safety of this formula.

Design: Controlled clinical trial.

Settings: Hong Kong during epidemic of SARS.

Subjects: Two cohorts of health care workers from 11 hospitals in Hong Kong, 1 using an herbal supplement for a 2-week period ($n = 1063$) and a control cohort comprising all other health care workers who did not receive the supplement ($n = 36{,}111$) were compared prospectively.

Interventions: Taking an herbal supplement for a 2-week period.

Outcome measures: SARS attack rates and changes in quality of life and influenza-like symptoms were also examined at three timepoints among herbal supplement users.

Results: None of the health care workers who used the supplement subsequently contracted SARS compared to 0.4% of the health care workers who did not use the supplement ($p = 0.014$). Improvements in influenza-like symptoms and quality of life measurements were also observed among herbal supplement users. Less than 2% reported minor adverse events.

Conclusion: The results of this pilot study suggest that there is a good potential of using Traditional Chinese Medicine (TCM) supplements to prevent the spread of SARS.

INTRODUCTION

Health care workers formed one of the most affected groups of the severe acute respiratory syndrome (SARS) epidemic that began in Hong Kong around March 12, 2003. As of June 2003, 19.5% of the 1755 confirmed or suspected cases reported in Hong Kong were attributable to health care workers, resulting in 6 fatalities (World Health Organization, 2003).

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has classified SARS as a disease related to *Wan Bing*, meaning "feverish diseases" in Traditional Chinese Medicine (TCM), based on the close resemblance of the two illnesses. Such respiratory ailments were so prevalent in ancient China that *Wan Bing* developed into a highly specialized branch of TCM, which can be traced back 500 years. According to the traditional Wan Bing precepts, influenza-like diseases can be divided into four stages: (1) fever development, (2) nasal symptoms, (3) fever and chills, and (4) hemoptysis (Lin et al., 2003). In Western medicine, the first two abovementioned stages may be viewed as symptoms that usually subside without treatment. The later stages represent more unusual conditions, when bronchitis and late pneumonia occur. Although there is no simple effective treatment for influenza in Western medicine, *Wan Bing* practitioners have had measurable success in containing the symptoms to the early stages. It is widely believed that the combined treatment regime of mainstream Western medicine supplemented with TCM, used by many patients with SARS (Chinese Center for Disease Prevention and Control, 2003), may have contributed to the relatively low mortality from SARS in China (Lin et al., 2003). Because SARS is a viral infection with symptoms that are similar to influenza, the use of a *Wan Bing* formula for prevention and treatment in early stage illness appears promising. The primary objective was to investigate the efficacy of an herbal formula in the prevention of SARS transmission among health care workers. The secondary objectives are to investigate quality of life (QOL) and symptomology changes among supplement users, and to evaluate the safety of this formula.

Table 1. Background Characteristics of the Herbal Supplement Users (n = 1063)

	Frequency	*Percentage (%)*
Age		
20–30 years	184	17.3
31–40 years	366	34.4
41–50 years	377	35.5
51–60 years	135	12.7
>60 years	1	0.1
Gender		
Female	829	78.0
Male	234	22.0
Occupation		
Nurse	485	45.6
Nonclinically trained support staff[a]	283	26.6
Doctors/allied health workers and others[b]	295	27.8
Location of Work		
Accidental and emergency unit	16	1.5
Intensive care unit	98	9.2
Infection ward	166	15.6
General ward	289	27.2
Orthopedics and Traumatology	48	4.5
Outpatient clinic	110	10.3
Administrative area	93	8.7
Other[c]	243	22.9
Hospital		
Hospital A	414	38.9
Hospital B	139	13.1
Hospital C	132	12.4
Hospital D	86	8.1
Hospital E	80	7.5
Hospital F	79	7.4
Hospital G	35	3.3
Hospital H	29	2.7
Hospital I	28	2.6
Hospital J	26	2.4
Hospital K	15	1.4

[a]General service assistant, health care assistant, ward assistant, workman, steward, operation theater assistant, blood-taking assistant.

[b]Doctor, dietitian, audiologist, radiographer, physiotherapist, occupation therapist, podiatrist, technician, research assistant, research assistant.

[c]Pharmacy, endoscopy unit, electrodiagnostic unit, telemedicine unit, information technology office, laboratories, X-ray, occupational therapy department, physiotherapy department, radiology department, prosthetic and orthotic, central office, admission office, rehabilitation, transportation, canteen, mortuary, central sterile supply department, health information center.

MATERIALS AND METHODS

The herbal formula

The formula combined two formulas that have commonly been used in the prevention and treatment of early-stage influenza-like symptoms: *Sang Ju Yin* (He et al., 1990a) and *Yu Ping Feng San* (He et al., 1990b). Two ingredients, noted in the modern herbal pharmacopoeia to have strong antiviral properties, were also added. The formula consisted of 12 herbs, namely Folium mori, Flos chrysanthemi, Semen armeniacae amarum, Fructus forsythiae, Herba menthae, Radix platycodonis, Radix glycyrrhizae, Rhizoma phragmitis, Radix astragali, Radix saposhnikoviae, Folium isatidis and Radix scutellariae. These herbs have been used for more than a thousand years and are considered safe for consumption because no significant adverse effects have been recorded (He et al., 1990a, 1990b). *Sang Ju Yin* and *Yu Ping Feng San* were chosen because the former was popular in southern China, whereas the latter was popular in the northern part. The former was also known to be "cold" while the latter was "warm." The combination, therefore, was expected to be more suitable for general consumption (for a period of 2 weeks) among people of different age and health status. In order to ensure high quality, the herbs were purchased from a reputed TCM supplier and prepared according to standard Good Manufacturing Practice (GMP; World Health Organization, 2000). These ingredients were boiled to form a decoction and then freeze-dried into pellets that could be easily reconstituted into a tea-like drink.

Subjects and data collection methods

Volunteers who were health care workers working in the 11 hospitals governed by the Hong Kong Hospital Authority who had been caring for patients with SARS were recruited to the study. All recruits were asymptomatic for SARS at the study's commencement. Exclusion criteria included: major medical illness, renal insufficiency, and hypersensitivity to Chinese herbal preparation. With informed consent, the health care workers received 14 packets of the herbal supplement free of charge and were advised to consume the one packet every day for 2 weeks. The herbal formula was distributed around mid-April 2003.

In Hong Kong, the last case of SARS among health care workers was reported on June 4, 2003. In order to address the primary research objective, herbal formula users, and a control group (consisting of all other non-user health care workers of the 11 hospitals) were prospectively followed between April 17, 2003 and August 17, 2003 to compare the proportions of health care workers in each cohort contracting SARS. These figures were cross-checked with the Hospital Authority's SARS registry database on August 17, 2003 to determine whether any of the supplement users contracted SARS after using the supplement. The SARS case definition used in this study followed the criteria for SARS cases used by Hong Kong Hospital Authority: radiographic evidence of infiltrates consistent with pneumonia, and current temperature higher than 38°C or a history of such at any time in the preceding 2 days, and at least two of the following: history of chills in the past 2 days, new or increased cough, or breathing difficulty, general malaise or myalgia, typical signs of consolidation, and known exposure. These criteria for cases are equivalent to the World Health Organization's case definition (Hong Kong Hospital Authority, 2003) for probable SARS cases (7). Research studies have shown that the prevalence of asymptomatic SARS among hospital workers (Chan et al., 2003) and general practitioners (Yu et al., 2004) was extremely low.

To address the secondary objectives, symptomology and QOL was assessed at three time points for the supplement users (just prior to commencing intake [day 0], 2 weeks after commencement of intake [day 14], and 2 weeks after cessation [day 28]) using three identical self-administered questionnaires. The mental health and vitality subscales of the Chinese version of the Short Form-36 (SF-36) which has been validated in Hong Kong, were used to measure aspects of QOL (Lam et al., 1998). The following influenza-like symptoms were assessed using a visual analogue scale (0 to 10): fever, chills, muscle pain, headache and "heavy feeling," cough, fatigue, rigors and "hot feeling" (feverishness). A number of *Wan Bing*-like symptoms suggested by a panel of TCM experts were also assessed (each classified as yes/no): thick tongue sign, sore and/or dry throat, sleeping problems, feeling "cold," "hot," or "humid." All adverse events were also recorded. The volunteers were instructed to fax the three questionnaires at the study's conclusion. A randomized control design was not used for this purpose because the study was conducted at the peak of the epidemic when the Hospital Authority wanted to offer the herbal supplement to as many frontline health care workers as possible. Of a total of 16,437 health care workers in the 11 hos-

Table 2. Comparison of the Job Composition of the Two Study Cohorts

Job category	*Supplement user cohort*	*Control cohort*
Nurses	485 (45.6%)	19,228 (53.2%)
Nonclinically trained support staff	283 (26.6%)	7235 (20.1%)
Doctors/allied health workers/others	295 (27.8%)	9648 (26.7%)
Total	1063 (100%)	36,111 (100%)

Table 3. Changes in Short Form-36 Mental Health and Vitality Quality of Life Subscales

	Mental health			*Vitality health*		
	Mean	*(SD)*	*Paired* t *test* p *value*	*Mean*	*(SD)*	*Paired* t *test* p *value*
Day 0	60.8	(9.89)		57.88	(11.89)	
Day 14	62.14	(9.25)		59.15	(11.77)	
Day 28	62.34	(9.38)		58.63	(11.92)	
Day 0–14			<0.001			<0.001
Day 14–28			0.284			0.019
Day 0–28			<0.001			0.010

SD, standard deviation.

pitals, 2601 received the herbal supplement, of which 1063 (40.9%) returned the questionnaires.

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Statistical analysis

The difference in the attack rates of SARS transmission occurring in the two cohorts was tested by the Fisher's exact test. Changes in the SF-36 mental health and vitality subscales and the influenza-like symptoms before and after the intake of the herbal supplement were tested for statistical significance by using paired *t* test and McNemar's test.

RESULTS

Background characteristics

The background characteristics of the subjects are summarized in Table 1. The distribution of the three types of health care workers (nurses, nonclinically trained support staff, doctors/allied health workers and others) of the two cohorts were comparable (Table 2).

Efficacy of SARS prevention

None of the 1063 herbal supplement users had contracted SARS, whereas the attack rate in the control group was 0.4% (64/15,374), ($p = 0.014$, one-tailed test, exact test).

Mental health and vitality quality of life subscales

Table 3 shows that there was a statistically significant improvement in mental health score between day 0 and day 14 ($p < 0.001$) and day 0 and day 28 ($p < 0.001$) although there was no significant improvement between day 14 to day 28 ($p = 0.284$). The vitality score also showed statistically significant improvements from day 0 to day 14 ($p < 0.001$) and from day 0 to day 28 ($p = 0.010$), although it decreased slightly from day 14 to day 28 ($p = 0.019$).

Influenza-like symptoms

The mean and standard deviations of the visual analogue scales for various influenza-like symptoms are summarized

Table 4. Changes in Visual-Analogue Scale Scores Referring to Western Medicine's "Influenza-Like" Symptoms Among Herbal Supplement Users

	Chill symptoms			*Rigor symptoms*			*Muscle symptoms*			*Headache & heaviness symptoms*			*Cough*		
	Mean	*(SD)*	*Paired* t *test* p *value*	*Mean*	*(SD)*	*Paired* t *test* p *value*	*Mean*	*(SD)*	*Paired* t *test* p *value*	*Mean*	*(SD)*	*Paired* t *test* p *value*	*Mean*	*(SD)*	*Paired* t *test* p *value*
Day 0	0.41	(1.35)	—	0.37	(1.18)	—	1.63	(2.22)	—	1.41	(2.14)	—	0.59	(1.27)	—
Day 14	0.35	(1.17)	—	0.34	(1.07)	—	1.46	(2.07)	—	1.23	(1.91)	—	0.52	(1.14)	—
Day 28	0.30	(1.08)	—	0.32	(1.09)	—	1.44	(2.12)	—	1.04	(1.81)	—	0.43	(1.09)	—
Day 0–14			0.035			0.170			<0.001			<0.001			0.016
Day 14–28			0.007			0.442			0.597			<0.001			0.001
Day 0–28			<0.001			0.121			<0.001			<0.001			<0.001

SD, standard deviation.

Table 5. Percentages of Subjects Having Symptoms That are Related to *Wan Bing*

Symptoms	Percentage (%)			McNemar Test p-value		
	Day 0	Day 14	Day 28	Day 0 vs. day 14	Day 14 vs. day 28	Day 0 vs. day 28
Thick tongue sign	47.3	42.9	40.5	<0.001	0.008	<0.001
Dry/sore throat condition	38.1	30.8	27.1	<0.001	0.003	<0.001
Irregular bowel habit	23.8	23.0	22.6	0.575	0.696	0.250
Loose/watery/hard stool condition	16.7	28.1	17.1	<0.001	<0.001	0.826
Not good/bad sleep condition	85.6	81.0	81.7	<0.001	0.494	<0.001
Feeling "cold"	19.8	16.0	14.6	<0.001	0.044	<0.001
Feeling "heat"	22.2	19.5	17.4	0.013	0.018	<0.001
Feeling "humid"	48.4	39.9	37.3	<0.001	0.028	<0.001

in Table 4. Subjects tended to have less symptoms on day 14 and day 28, compared to day 0 ($p < 0.05$), except for rigors symptoms (day 14 and 28, $p > 0.05$) and fever symptoms (day 28, $p > 0.05$). From day 14 to day 28, continuous improvement was found for the following symptoms: chills, cough, fatigue, and headache and feelings of "heaviness," ($p < 0.05$).

TCM symptoms related to Wan Bing

From Table 5, it can be seen that from day 0 to day 14 and from day 0 to day 28 each of the listed symptoms except the bowel habits and stool condition symptoms improved. The prevalence of sore/dry throat conditions decreased from 38.1% to 27.1%. The percentage of respondents feeling "humid" decreased from 48.4% to 37.3% ($p < 0.01$). Between day 14 and day 28, the prevalence of all symptoms continued to decrease, except for irregular bowel symptoms and sleeping problems.

Adverse events

Of the 1063 respondents, none reported serious adverse events and only 19 (1.8%) reported any minor adverse events, including diarrhea, sore throat, dizziness, and nausea. Of these respondents reporting adverse events, 9 ceased supplement use, 3 halved the dosage, and the rest continued using the herbal formula as prescribed. The details of the reported adverse events are summarized in Table 6.

DISCUSSION

To the authors' knowledge, this is the first study to explore the possibility of using a TCM supplement to prevent SARS in a high-risk population. This analysis has the strength of using a prospective cohort design and use of the actual SARS attack rates as the primary outcome measure. Such a large-scale study is unique and possibly could not now be repeated in the future unless another large-scale outbreak occurs. Because of the heightened concern over breakthrough SARS transmissions among health care workers at the time of the study, there was strong motivation to provide them with the highest degree of protection. Hence, a randomized controlled trial design was not feasible. Nevertheless, the job composition of the two cohorts was comparable. Both cohorts were at high risk of contracting SARS and the high numbers of nosocomial transmissions in Hong Kong allowed such a comparison to be made. Although serologic tests were not conducted on asymptomatic health care workers to confirm their SARS seronegativity, other recent seroprevalence studies reported very low prevalence of asymptomatic cases in the same population of health care workers

Table 6. Details of Adverse Events

Subject	Adverse event
1	Diarrhea, headache, dizziness
2	Diarrhea, headache, dizziness
3	Diarrhea
4	Constipation, sore throat, cold sore
5	Diarrhea, dizziness
6	Dizziness
7	Sore throat
8	Sore throat, fitful sleep with many dreams
9	Insomnia
10	Palpitation
11	Low-grade fever
12	Sore throat
13	Headache, nausea
14	Diarrhea
15	Fever and sweating
16	Dizziness, nausea, hand shaking, bowel gas pain
17	Irregular menstruation
18	Malaise
19	Diarrhea, stomachache, skin allergy

(Chan et al., 2003; Ip et al., 2004), lending credence to the observed differential attack rates between the two cohorts.

The study results suggest that there is a potential for using TCM supplements to prevent SARS. The QOL and symptomology data further suggest that the herbal supplements were beneficial. The claim is also supported by the results of another study documenting an increase in the immune function that persisted for a 2-week period among 37 laboratory technicians with SARS after cessation of using the same herbal supplement treatment regime (Poon et al., 2003).

Although the study was preliminary in nature, using TCM to treat ailments is common in China. It has been noted that approximately 13.5% of the general public in Hong Kong were using TCM on a frequent or an occasional basis (Lau et al., 2001). During the SARS epidemic, 40.5% of the general public believed that TCM was efficacious for SARS prevention (unpublished data). Furthermore, Chinese medical officials suggest that TCM may be used to treat SARS and that some herbal formulae may have protective effects against the virus (Chinese Department of Health, 2003).

Herbal formulas had also been reported for being effective in preventing diseases such as influenza but few of these studies were randomized clinical trials (RCT) (Yamada et al., 1998). Likewise, it is fully acknowledged that the major limitation of this study is that this was not a randomized study. During the emerging phase of the epidemic, it was not possible to measure the risk level of all subjects, which included the nature of tasks, the number of patients, and use of personal protective equipments, etc. Other alternative explanations or confounding bias may therefore exist. However, it is unlikely that those who were at lower risk of contracting SARS were more likely to volunteer to use the herbal supplement; it is expected that the reverse may be true (i.e., that those who were at higher risk would have a stronger motivation to use the herbal supplement). Therefore, the zero incidence observed in the herbal supplement cohort should not have resulted from a lower risk exposure to SARS. The direction suggests that any existence of participation bias should not have confounded the observed results. Again, the RCT study design was not feasible because the study was conducted during the peak of a unique SARS outbreak. The cohort study design should thus be a reasonable alternative under the circumstance. The response rate was another limitation as only slightly more than 40% or so of those who received the herbal packets returned the questionnaire. By checking the SARS registry, the investigators confirmed that none of the 2601 health care workers who received the herbal supplement had contracted the virus. The 2097 nonresponders were then regarded as nonusers in the analysis, rendering a conservative estimate of the differential SARS attack rate. Hence, moving nonrespondents who were actual herbal supplement users to the supplement user cohort, would result in an even more marked difference in SARS attack rates between the two cohorts. In the most extreme scenario of all of the nonrespondents being supplement users, the attack rates for the supplement users and control group would be 0% and 0.46%, respectively (exact test, $p < 0.001$). One other limitation of this study was the absence of QOL and symptomology assessment in the control cohort, making interpretation of these results difficult, because other potential confounders might exist. The consistency of the study results, however, suggests that the supplement has a potential of bringing about beneficial effects on symptom control and QOL.

There are few studies comparing the effectiveness of SARS preventive measures (Lau et al., 2004) and none examining the use of nutritional supplements in SARS prevention. Because the herbal formula is safe and affordable ($8.50 for a 2-week supply), it can be considered as a SARS prevention option. Large-scale controlled trials for influenza prevention in different high-risk groups, such as health care workers and elderly nursing home residents, may be warranted.

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