EFFECTS OF TRADITIONAL CHINESE MEDICINE SHANG HAN LUN FORMULAS IN THE TREATMENT OF INFLUENZA LIKE ILLNESS CONDITION (ILI)

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RESUMO

A gripe é uma doença infecciosa, aguda, transmissível que durante uma epidemia pode causar elevada morbilidade e mortalidade. Desde 1949, a OMS estabeleceu uma rede internacional de vigilância da actividade gripal feito pela integração da informação virológica per *se* ou em combinação com a informação clínica obtida em pacientes diagnosticados com a *"doença semelhante à influenza" ou* "*sindroma gripal".*

A Medicina Tradicional Chinesa (MTC) considera a *influenza* uma patologia externa causada por factores patogénicos e desenvolveu há milhares de anos um sistema especialmente orientado para a sua prevenção e tratamento descrito no *"Shang Han Lun"*. O objectivo deste estudo foi o de avaliar os efeitos de fórmulas clássicas do *Shan Han Lun* prescritas de acordo com os seus princípios *versus* regimes convencionais correntes*,* no tratamento da *Sindroma Gripal* em pacientes que recorrem ao tratamento da MTC*.*

Sessenta pacientes da Escola de Medicina tradicional Chinesa e de Clínicas de Profissionais da Associação Portuguesa de Acupunctura e MTC, em Lisboa que apresentavam síndroma gripal foram distribuídos aleatoriamente pelo Grupo Experimental e Controlo. Após os primeiros três dias de início da patologia foi observado uma taxa de recuperação clínica significativamente diferente no grupo experimental *versus* controlo e verificado que as fórmulas clássicas do *Shang Han Lun* podem tratar a síndroma gripal se utilizadas de acordo com o método de decisão clínica implícito no Clássico da MTC.

Palavras- Chave–Medicina Tradicional Chinesa/ Medicina Herbal Chinesa/ Shang Han Lun/ Influenza/Fórmulas clássicas da Medicina tradicional Chinesa.

ABSTRACT

Influenza is an acute respiratory communicable disease which, during epidemics, can cause high morbidity and mortality. Since 1949, WHO established an international network for the surveillance of influenza mainly based on sentinel physician's report of clinical cases of ILI (influenza-like illness) to a central registry. Traditional Chinese Medicine (TCM) considered this condition as an externally contracted disease caused by pathogenic factors and have developed from thousands years ago a rich system for its prevention and treatment expressed in the *"Shang Han Lun"*. The purpose of this study was to assess the effects of Chinese medicinal classic formulas according to TCM principles of *"Shang Han Lun"* in treating Portuguese patients with established diagnosis of ILI condition by comparing it with western current treatment regimens.

Sixty patients from the Clinic of TCM College of Lisbon and from the clinical sets of Portuguese Association of Acupuncture and TCM in Lisbon region that have ILI condition were randomized allocated to an Experimental and a Control Group. After the first three days it was observed that the recovery rate was significantly different in experimental versus control group and classic formulas of "*Shang Han Lun"* can treat ILI conditions if used with the clinic decision through method that is implicit in this Classic monograph.

Keywords –Traditional Chinese Medicine/ Chinese herbal medicine/ Shang Han Lun/ Influenza/Chinese classic formulas

INTRODUCTION

According to Western Medicine the flu (influenza), bird flu and common cold are respiratory infection diseases caused by a variety of viruses that present different main symptoms and mortality rate. The common flu and cold were usually mild diseases lasting 3 to 7 days when the patient could have enough rest, drink fluids and sweat. However in the last years, people have different life habits and the disease spreads through communities creating an epidemic. The rapid diffusion of epidemics and pandemics turns clear the need for clinical/epidemiological and virological surveillance, at local, regional and world level.

WHO established an international network for the surveillance of influenza since 1949 (WHO, 2000). EISS project in Europe. This is done by the Integration of virological information alone or with that obtained in patients diagnosed with ILI condition (influenza-like illness or flu like syndrome) (Fleming et al., 1995 cit. in EISS, 2008). EISS studies found a good match between the clinical data and laboratory reports of influenza collected by physicians only during peak season levels of ILI (3 to 4 months) activity in a given country.

Clearly, it has been difficult to establish common rules for clinical definitions of influenza in different countries with different health systems and organizations. However there have been a tendency of the European EISS members to define an ILI case by its general criteria which are: sudden onset of fever > 38°C, with respiratory (i.e. cough, sore throat) and systemic symptoms (headache, muscular pain) or by the criteria for Acute Respiratory Infection (ARI) which are: sudden onset of respiratory symptoms, accompanied by fever and headache in the absence of other diagnosis. Traditional Chinese Medicine (TCM) considered influenza as an externally contracted disease caused by pathogenic factors entering the body from out side and have developed from thousands years ago a complete and rich system for their treatment. In the prevention and in the treatment of this disease TCM has a very effective treatment according to the pattern of symptoms differentiated in each patient by the TCM diagnose process. The clinical experience in Portugal as in China also demonstrates that there is not a unique formula that can fit all the influenza-like TCM-patterns presented by the patients.

In the same way in more than 300 clinical trials of Chinese medicinal herbs for influenza systematically reviewed by Chen XY et al. (2005) showed that TCM has a treatment for influenza and that TCM doctor's have good results in treating this condition. However, the constituents of the prepared formulas are modified according to each patient TCM-patterns diagnosed which make difficult to compare results or to know the more adjusted patent TCM formulas to treat ILI in other regions or in other patients.

So the purpose of this study is to assess the effects of Chinese medicinal classic formulas according to TCM principles for treating people of all ages with established diagnosis of ILI defined by the International Classification of Health Problems in Primary Care and standardized by the Portuguese Health Government. It is also interest of this study to validate a diagnostic tool to characterize the main TCM syndromes corresponding to ILI syndrome according to *Shang Han Lun* differentiation system in the flu season of 2007/2008.

In comparing groups intended for treatment with Chinese classic formulas and groups allocated to the treatment with western current treatment regimens, the following hypotheses are tested:

1. Is there any difference in the number of people cured at the end of the third day?

2. Is there any difference between Chinese classic formulas and current treatment regimens in the clinical recovery and outcomes?

THEORETIC RESEARCH

TCM characterization of external disease caused by cold damaged

In Chinese medicine, cold is a disease caused by exogenous factors, namely pathogenic wind-cold, invading the body. It manifests as blocked or runny nose, sneeze, cough, headache, aversion to cold, fever, general discomfort, superficial pulse.

Cold that presents symptoms of more serious nature, and that transmits more widely and rapidly, is known as influenza. Influenza appeared by the combination of abnormal climates, pathogenic factor and individual reaction to that. It causes more severe illness and may deteriorate into heat syndrome or become complicated by

diseases in other organs. Common symptoms include aversion to cold, chills, fever, body temperature up to 39°C - 40°C, general body ache and malaise, cough, sneeze, sore throat, nasal discharge and obstruction as have been seen (Nanjing, Internal Medicine, 2002 and Hong Kong Chinese Medicine Division, 2005).

Generally the main principle applied in the treatment of influenza is *"to expel the pathogenic factor, relieving the exterior syndrome and resolve the interior condition"*, following TCM diagnose. Chinese medicine practitioners differentiate syndromes and prescribe medicines according to the pathogenic causes, characteristics of symptoms and strength of individual *Zheng Qi*, taking into account the seasonal prevalence of influenza and characteristics of climates.

This study, instead of describing the common syndromes of influenza and the usual treatments as is presented in TCM internal medicine textbooks try to follow the thought and clinical experience transmitted by *"Shang Han Lun"* to analyse all the main possibilities of patterns of unbalanced related with ILI and the main prescriptions to treat this condition according.

In *"Shang Han Lun"* there is three main kind of differentiation: 1) the six syndrome differentiation; 2) the eight principles; 3) the decoctions differentiation. However all these three stages of the differentiation process are much closed related and directed to the clinical treatment of these diseases. Differentiation is not only based in the strength or weakness of the pathogenic factor, but also in the patient's constitution and *Zheng Qi* that will determine the progression of the disease. To differentiate the trends of development and the changes in disease the pulse and signs are the main criteria.

In the broad meaning of cold damage the influenza is differentiate into two types: wind-cold and wind-heat, however the pathogenic factor related with influenza, as is referred by literature transmits more widely and rapidly and presents symptoms of more serious nature. This means that it is important to profit the millenary clinical experience abstracted in *"Shang Han Lun"* to prevue, in advance, the possible changes of pathogenic factors when invading the human body.

Portugal has a temperate climate and the peak of influenza occurs in autumn and winter seasons which mean that is usual that Cold, in the strict sense, may be involved in the initial phase of the ILI condition. According with the Chinese clinical

experience it's common to observe cases of influenza beginning by a cold pathogenic factor rapidly changing to other *Taiyang* patterns concurrent or transferred, described in *"Shang Han Lun"* line's. Table 1 shows a decision tree based on *"Shang Han Lun"* and *Cheng Song Yu* and *Li Fei* (1996) that allows us to visualize the main clinical decision thought present when we are deciding the best prescriptions that release the exterior condition as is the case of ILI.

Table 1 - Clinical decision tree based on the prescriptions that release the exterior of the *"Clinical Guide of Herbs and For mu la s"* by *Cheng Song Yu* and *Li Fei* (1996)

Formulas that release exterior	Pattern type	Associated conditions	Prescriptions
Wind Cold	1.Exterior Excess → 1.a) Excess – mild, early stage	Cold mild	*Cong Chi Tang*
	1. b) Excess – severe →	Cold	***Ma Huang Tang***
		Wind-Cold-Damp	*Jiu Wei Qiang Hu Tang*
		Qi Stagnation Torax Distension	*Xiang Su San*
		Interior Heat	***Da Qing Long Tang***
		Water-Phlegm Retention	***Xiao Qing Long Tang***
	2.Exterior Vacuity → 2.a) Vacuity →	Wind	***Gui Zhi Tang***
		Stiffness neck and costal region	***Gui Zhi Jia Ge Gen Tang***
		Cough and wheezing	***Gui Zhi Jia Hou Po Tang***
		Yang Vacuity	***Gui Zhi Fu Zi Tang***
		Qi Vacuity	***Gui Zhi Jia Ren Shen Tang***
	3. Wind-Cold Turning Heat →	Concurrent and transferred patterns of Wind-Cold including *Taiyang* *Shaoyang* *Yangmin*	Different prescriptions according to the evolution of the pathogenic factor in each individual (see Table2)
Wind Heat	*Wei Qi* level	Cough	*Sang Ju Yin*
		Deficient *Ying Qi* and *Jin Ye*	*Yin Qiao San*
	Toxic heat →	Early stage meales or rashes	*Sheng Ma Ge Gen Tang*
Wind-cold	Interior Vacuity →	*Qi* and *Yang* Vacuity Lesser *Yin* syndrome	***Ma Huang Fu Zi Xi Xin Tang***
Wind Heat	Interior Vacuity →	*Yin* and *Xue* Vacuity	*Cong Bai Qi Wei Yin*

The main divisions seen in this Table are based on TCM classics, the prescriptions are those that release exterior condition prescribed in accordance with

the Six Channels or Four Levels patterns theory and in accordance with the possible observed associated conditions as are pointed out by *Cheng Song Yu* and *Li Fei* (1996). Regarding Portuguese conditions and the research question of this study it was selected from this table (Table 1) the formulas (in bold) that could treat the main standard conditions related with ILI in Portugal. The selection is based in 1) *The Clinical Guide of Herbs and Formulas"* by *Cheng Song Yu* and *Li Fei* (1996); 2) *"The Formulas & Srategies"* by *Bensky D.* and *Barolet R.* (1990); 3) The translation and comments on *"Shang Han Lun"* written by *Zhang Zhong-Jing* (*Zhang Zhong-Jing* compiled and translated by *Luo Xiwen*, 1993; *Zhang Zhong-Jing* translation and commentaries by Craigh Mitchell, Feng Ye & Nisel Wiseman (1999); 4) The discussion and orientation by the adviser Professor of Nanjing TCM University Professor Chunxiang Zhou about the Portuguese research conditions and available Chinese classic formulas.

As can be observed the most important exterior conditions related with ILI can be treated with "S*hang Han Lun"* formulas, except Wind-Heat conditions in the *Wei Qi* level, that are usually treated according to the Classic *"Wei Bing Xue" – "Treatise of Warm Disease".*

So, after seeing the general approach to the possible conditions of exteriorcontracted diseases it is possible to construct a decision table based on "Shang Han *Lun"* differentiation process as is presented in Table 2. In this table are considered:

1. The level or pattern of the condition or it's localization which is defined by the channel or channels involved in the disease;
2. The depth of pathologic changes which means to observe if the condition is in the channels or in the Zangfu - Fu or Zang (usually the Lung in this disease);
3. The status of Zheng Qi and Xie Qi confrontation which is related with the constitution of the patient and the strength of pathogenic factor and it's relations;
4. The initial nature of the pathogenic factor related with the six pathogenic factors and its combinations;
5. The nature of the condition and its transformations presented by the patients;
6. The key symptoms, between others, presented in the Diagnostic tool (Attachment 1) which determines all the differential process that finishes with the choice of the best formula to treat the patient condition.

Table 2 - Shang Han Lun differentiation process related with the possible patterns and formulas to treat the ILI condition caused by Wind-Cold

Level/ Transformation pattern Category of disease (*Yin*	**Exterior/ Interior** (Depth of pathological changes)	**Excess/ Vacuity** (Status of confrontation of *Zheng Qi Xie*	**Patogenic factor** (Initial Pathogenic factor)	**Heat/Cold** (Nature of the disease)	**Key symptoms**	**Prescriptions** (Line - Song version)
Tai Yang	Exterior	Excess	Cold	Cold	Aversion to Cold, no perspiration	*Ma Huang Tang* (Line 35)
Hebing (Tai Yang concurrent	Exterior Interior	Excess	Cold	Wind Cold Heat	Aversion to cold, no perspiration. Restlessnes	*Da Qing Long* Tang (Line 38)
Hebing (Tai Yang concurrent	Exterior Interior	Excess	Cold	Cold Retention of water-	Aversion to cold, nausea, cough, asthma, tight – tense pulse	*Xiao Qing Long* tang (Line 40)
Tai Yang	Exterior	Vacuity	Wind	Wind	Perspiration and fever	*Gui Zhi Tang* (Line 12)
Hebing Tai Yang concurrent	Exterior	Vacuity	Wind	Wind	Perspiration and fever and stiff neck and back	*Gui Zhi Ge Gen Tang* (Line 14)
Hebing Tai Yang concurrent	Exterior	Vacuity	Wind	Wind	Perspiration and fever and dyspnea (asthma)	*Gui Zhi Jia Hou Po Xing Zi Tang* (Line 18)
Hebing Tai Yang concurrent pattern *(Tai*	Exterior/ Interior	Vacuity	Wind	Wind turned Heat Vacuity cold	Perspiration and fever week and floating pulse. *Qi* vacuity	*Gui Zhi Ren Shen Tang* (Line 163)
Shao Yang Pattern	Half exterior/ Half interior	Excess	Cold	Alternate Cold and Heat	Alternate chills and fever, opression sensation in chest and costal region,	*Xiao Chai Hu Tang* (Line 37)
Hebing Tai Yang, Shaoyang concurrent pattern	Half exterior/ Half interior	Excess	Cold	Un resolved exterior pattern with mild cold in the exterior mild heat in the interior	Continuous fever, light chills, severe pain in the extremities and joints, slight náusea and fulness and distension of epigastrium. Both *Shao*	*Chai hu Gui Zhi Tang* (Line 146)
Bianzheng Transmuted patterns of *Tai Yang*	Exterior Interior	Excess	Cold	Cold transfomed in Heat in the Lung	Excess heat obstructing lung, asthma, .cough, yellow phlegm, thirst for cold drinks.	*Ma Huang Xinren Gancao Shigao Tang* (Line 63)
Yang Ming	Interior	Excess	Cold	Exuberant dryness Heat	High fever, great thirst, profuse perspiration (Fever without chills)	*Bai Hu Tang* (Line 176)
Bianzheng Tranmuted patterns of *Tai Yang (Yang*	Exterior Interior	Excess	Heat	Cold transformed in Interior Heat	Acute Heat-type Watery diarrhea	*Ge Gen Huangqin Huanglian Tang* (Line 34)

EXPERIMENTAL RESEARCH

Case resource

Selection criteria

Patients were selected from the Clinic of TCM College of Lisbon and from the clinical sets of Professionals of the Portuguese Association of Traditional Chinese Medicine in Lisbon region that (1) have six of the eight symptoms of the influenza-like illness condition as defined by the International Classification of Health Problems in Primary Care and adopted by the General Direction of Health in Portugal and (2) are in the first day (24hours) of complain. adopted by the General Direction of Health in Portugal that are: sudden begin 12h; Cough; Chills; Fever (38ºC); Fatigue/ prostration; Muscle aches/body generalized pain; Nasopharyngeal inflammation without other respiratory signs ; Has been exposed to some patient with flu, and are in the first day (24hours) of complain.

Experimental Group – Group 1

Thirty (30) patients, 9 males (48,00 21,66 years of age) and 21 females (42,19 16,76 years of age) from the Clinic of TCM College of Lisbon and one clinical set of Lisbon region.

Control Group – Group 2

Thirty (30) patients, 8 males (53,63 18,49 years of age) and 22 females (50,05 18,14 years of age) from the Clinic of TCM College of Lisbon and one clinical set of Lisbon region.

Randomized trials for Control and Experimental Groups

Each patient with influenza-like illness had a number and a group distribution according to a computer generated allocation sequence from a random number table. The patients attributed to group1 (experimental or MTC) were treated with patent traditional Chinese "*Shang Han Lun"* medicinal formulas. The patients attributed to group 2 (control or western medicine) were treated with western current treatment regimen, self-medicated or prescribed by western doctor or pharmacist. In each center were used opaque sealed envelopes that were distributed by a non-involved professional.

Experimental design

1. Development and validation of a diagnostic tool for externally contracted diseases caused by cold in the Lisbon region of Portugal according to "*Shan Han Lun"* differentiation process.
2. Development of two types of follow-up sheet for patient and professional registration.
3. Application of the diagnostic tool and the registration sheet at least to sixty patients with influenza-like illness syndrome during 1 to 10 days.
4. Application of the TCM differential diagnose to 60 cases, prescription of the appropriated herbal traditional Chinese formulas to thirty of them and counseling the other thirty to utilize the western current treatment regimen or visit their western family doctor, according to the attributed number.
5. Study the case evolution by two process:

    a. By a personal registration done by patient.

    b. By the clinical assessment done by professionals.

In the following process have been observed as outcomes:

Rate of recovery (usually named clinical recovery)

Symptoms and clinical manifestations of influenza-like illness completely cleared and body temperature returned to normal within one to three days after the administration (expressed in days).

The effectiveness of the prescription or the treatment regimen:

- Marked improvement – Most of clinical symptoms of influenza cleared and body temperature returned to normal within one to three days.
- General improvement – Partial symptoms or manifestations of influenza are not improved neither lightened nor deteriorated and body temperature falls within three days.

- No improvement – Symptoms or manifestations of influenza are not improved or may even have deteriorated (e.g. complications may occur) after three days.

The side effects – Any adverse events resulting from the treatment as: uncommon response and results causing discontinuation of treatment.

Marked, general or no improvement of the clinical signs and symptoms of TCM six channels differentiation process related with influenza like illness were observed every day by each patient and in the first day of treatment by a TCM doctor and between the third and tenth day by another TCM doctor in order to check and control the patient evolution and registration in both groups.

Treatment instruments

The Diagnostic tool for external contracted disease caused by cold according to "*Shang Han Lun*" differentiation process and the follow-up registration sheet (Attachment 1,2) were applied and corrected by Portuguese professional expert's and validate by two experts of *Shan Han Lun* one from Nanjing TCM University other from Chengdu University.

Treatment Procedures

The diagnostic tools are applied in the first session of treatment and after three days to ten days in each clinical timetable. The follow-up registration sheet answered by the professionals is given and applied three to ten days after the first treatment. The follow-up and the registration sheet answered by the patient are given in the first day of treatment and filled 1-10 days after the first consultation done by TCM professionals.

The herbal prescription or western treatment is done after the first day of the diagnostic process and must be taken in the closest hour possible to that act. The compliance is assessed by the professionals and by the patients in the follow-up registration sheets

Herbal Treatment

The plants of the formulas *Ma Huang San*, *Gui Zhi San, Xiao Chai Hu San, Da Qing Long San, Ma Huang Xingren Gancao Shigao San, Ge Gen Huang Qin Huang Liang San and Chai hu Gui Zhi San* were bought in soluble granules to the *© United Herbs Ltd* and prepared by a TCM professional. The granules of the formula are given to the patient in a bag for each day. They have to warm the purified water and dissolve the granules of all formula plants for a day and take the solution 3 times a day between meals during 1to 3 days for *Ma Huang* and 3 to 7 days for the others, according to the symptoms remission. The formulas follow the plant dosage indicated in Shan Han Lun, translated by Luo Xiwen (1993)

Treatment Methods

Each diagnostic tool and registration sheet of the same patient is centralized and renumbered by a non-medical person and the data extracted by the same person. The following up treatment was not done by the TCM specialist that has done the first consultation in both groups. The patients know what kind of treatment they are doing but don't know the research project objectives.

Quantitative analyses

Descriptive statistical analysis is used to calculate the mean, standard deviation of the quantitative variables presented or frequency, percent and valid percent of the nominal or ordinal variables. T-Student test is used to compare the quantitative variables of the two independent samples after verifying its normal distribution by Kolmogorov Smirnov test and homogeneity by Levene's Test for Equality of Variation. If the variables don't follow a Normal distribution, as happen frequently with new variables resulting by the sum of several different sources, it is used the Mann- Whitney U test for independent samples and the Wilcoxon matched pairs test for the same sample measured in two different conditions.

The Chi squared test is used to compare independent samples in relation to proportions obtain in a qualitative variable or to measure the association of two qualitative variables with the correction of Exact Fisher test when more than 25% of expected frequencies are 5. The P obtained by this test is also used, since the sample is small. The Pearson correlation Test is used to verify the nature and strength of the

association among the different variables. The variable plan and all the statistical analyses are done using the Statistical Tool *SPSS.13.0*. The significance level adopted for all the inference statistical test is 5% (p≤0,05).

Qualitative analysis

The qualitative analysis deals with the characterization of the flu syndrome according to TCM and the data collected by the diagnosis process. In this analysis was observed: The main syndromes of six channels differentiation related with the influenza-like illness condition in the year 2007/2008 and the main Chinese classic formulas indicated to their treatment.

EXPERIMENTAL RESULTS AND DISCUSSION

Almost all cases of this study have been diagnosed in the influenza peak period of 2007/2008, so they have an increased probability of representing this condition as can be observed when comparing the Figure 1 with the one published by Portuguese Health Observatory about *Influenza activity in Portugal in 2007/2008* (ONSA, 2008).

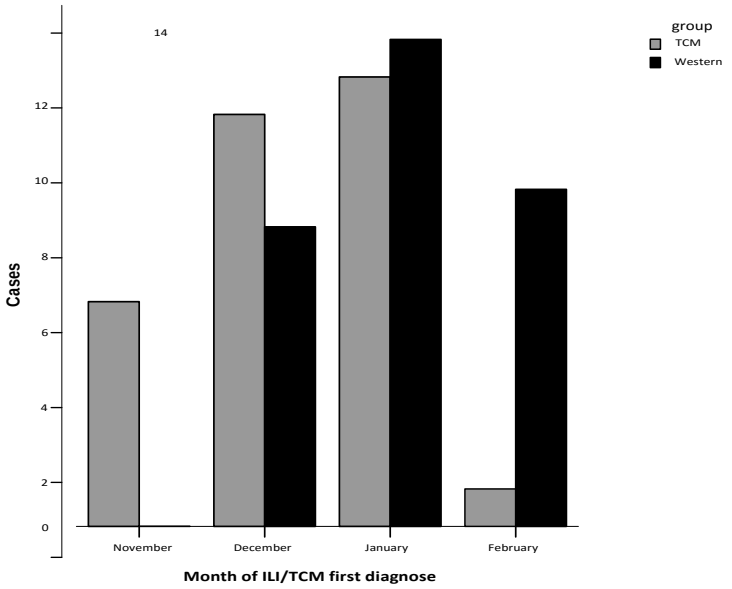

Figure 1 – Randomized allocation distribution of the two groups in the peak season of influenza 2007/2008.

The characterization variables of both groups that are related with the definition of ILI case are presented in Table 3. All subjects confirm the sudden onset of the disease and have, at least one episode of temperature above 38ºC. As these nominal variables are used to select the ILI cases, it is important to know if there are significant differences in

their proportions between the two groups, before the treatment regimens being applied.

Table 3 – Frequency, percent and valid percent of nominal variables related with influenza-like illness in experimental and control group.

	Experimental			Control		
General Pain						
No	12	40,0	40,0	7	23,3	23,3
Yes	18	60,0	60,0	23	76,7	76,7
Chills						
No	0	0,0	0,0	0	0,0	0,0
Yes	30	100,0	100,0	30	100,0	100,0
Fever*						
No	0	0,0	0,0	0	0,0	0,0
Yes	30	100,0	100,0	30	100,0	100,0
Throat pain						
No	21	70,0	70,0	16	53,3	53,3
Yes	9	30,0	30,0	14	46,7	46,7
Stuffy nose						
No	5	16,7	16,7	3	10,0	16,7
Yes	25	83,3	83,3	27	90,0	83,3
Cough						
No	14	46,7	40,0	7	23,3	23,3
Yes	16	53,3	60,0	23	76,7	76,7
Fatigue						
No	1	3,3	3,3	1	3,3	3,3
Yes	29	96,7	96,7	29	96,7	96,7
Exposed flu						
No	19	63,3	63,3	16	53,3	53,3
Yes	11	36,6	36,6	14	46,7	46,7

*38ºC

Table 4 – Observed and expected values for the nominal variables muscle aches/body generalized pain, stuffy nose, throat pain, cough and exposed to patients with flu.

		Experimental	Control	Chi-square	Level of significance
General Pain					
No	*O*	12	7		
	E	9,5	9,5	0,23	0,09
Yes	*O*	18	23		
	E	20,5	20,5		
Stuffy nose					
No	*O*	5	3		
	E	4,0	4,0	0,448	0,23
Yes	*O*	25	27		
	E	26,0	26,0		
Throat pain					
No	*O*	21	16		
	E	18,5	18,5	0,184	0,29
Yes	*O*	25	27		
	E	11,5	11,5		
Cough					
No	*O*	14	7		
	E	10,5	10,5	0,058	0,04
Yes	*O*	18	23		
	E	20,5	20,5		
Exposed to flu					
No	*O*	19	16		
	E	17,5	17,5	0,432	0,15
Yes	*O*	11	14		
	E	12,5	12,5		

The Chi square test and Fisher exact test shows no significant differences for these variables in the proportions of patient's symptoms in group 1 and 2, except for Cough as can be seen in Table 4.

As age can, also, be a factor that can influence the results between the two groups, they are compared in relation to this variable. Student T test shows no differences in the means of the variable patient's age of the two groups (Table 5). There are also no differences in the proportions of male and females (Table 6) and in the flu vaccination between the experimental and control groups (Table 7).

Table 5 Mean and standard deviation of the variable age in experimental and control group. Level of significance related with T-Student test

Age	Mean SD	T de Student	Level of significance
Experimental	43,93 18,17	1,51	0,14
Control	51,00 17,99		

Since the two groups are not significantly different in the beginning of treatment in relation to the symptoms that define ILI and in relation to the variables Age, Sex and Vaccination, that could influence the results of treatment, it is possible to verify, now, if they differ significantly in the rate or clinical recovery expressed in days, the main objective of this research.

Table 6 – Observed and expected values for the nominal variable sex in experimental and control group

Sex		Experimental	Control	Chi-square	Level of significance
Male					
No	*O*	9	8		
	E	8,5	8,5	0,77	0,5
Female					
Yes	*O*	21	22		
	E	21,5	21,5		

O – Observed values; *E* – Expected values

Table 7 – Observed and expected values for the nominal variable exposition to flu in experimental and control group

Vaccination		Experimental	Control	Chi-square	Level of significance
No	*O*	19	16		
	E	17,5	17,5	0,43	0,15
Yes	*O*	11	14		
	E	12,5	12,5		

Clinical recovery

The clinical recovery of symptoms, clinical manifestations of influenza-like illness completely cleared and body temperature returned to normal, in three days after the administration of the treatment regimens are presented and compared in Table 8 and 9. The variable rate of recovery distribution in experimental group is highly skewed showing no normal distribution so the Mann-Whitney Test is used for all clinical recovery analyses.

Table 8 - Mean and standard deviation of variable rate recovery (expressed in days), in experimental and control group.

Rate of Recovery RR	Experimental	Control
Mean SD	2,95 2,61	8,57 3,59

Table 9 - Mean and Sum of Rank values of the variable rate of recovery of experimental (group 1) and control (group 2) expressed in hours

	Experimental	Control	Mann-Whitney U	Level of significance
Mean Rank	18,52	42,48		
Sum of Ranks	555,50	1274,50		
			90,50	0,000

As can be observed in Table 9 there are significant differences between the mean rank values of the two groups ($p<0,001$) which means that there is a significant tendency for the level values of the variable clinical rate of control group exceed the experimental one. This also shows that the control group have a significantly slower ($p<0,0001$) recovery rate RR =8,57 3,59 when compared with the experimental one 2,95 2,61.

The effectiveness of the treatment regimen:

Although the two groups presented a normal distribution for the variable sum of symptoms and signs in the first day of treatment this doesn't happen for the third ant tenth day, so the Mann-Whitney Test is used to analyse this variable in these three different considered moments. As can be observed in Table 10 there is a significant tendency ($p<0,05$) for the level values of the variable sum of symptoms and signs in

the control group(14,03±3,44) exceed the experimental one (12,27±3,93). However, after the first three days there was a more significant tendency (p<0,001) to the level values of the variable sum of symptoms and signs in the control group exceed the experimental one (11,90±4,99 to 4,10±3,62 for the control and experimental group respectively in the third day of treatment and 1,40±1,85 to 0,10±3,05 for the control and experimental group respectively in the tenth day of treatment).

Table 10 - Mean and Sum of Rank Mann-Whitney U value and significance level values for the variable sum of symptoms and signs of experimental (group 1) and control (group 2) before, after 3 and 10 days of treatment regimens

Symptoms	Group	Num	Mean Rank	Sum Ranks	U	p
Initial	1	30	26,08	782,50		
	2	30	34,92	1047,50	317,500	0,049
After 3 days	1	30	18,52	555,50		
	2	30	42,48	1274,50	90,500	0,001
After 10 days	1	30	24,85	745,50		
	2	30	36,15	1084,50	280,500	0,001

After 3 days, it was observed a marked improvement of the sum of clinical symptoms and signs in the experimental group (recovering of symptoms and signs from 368 to 123) and a general improvement in the control group (recovering of symptoms and signs from 421 to 357).

Table 11 - Mean and standard deviation of variable sum of symptoms before and after 3 and 10 days of treatment regimen in experimental and in the control group. Level of significance related with T-pars and Levene Test

	Group 1			Group 2		
	Before	After 3 days	p	Before	After 3 days	p
Syntoms	12,27±3,94	4,10±3,62		14,03±3,44	11,90±4,99	
Mean Rank		15,50			11,00	
Sum of Ranks		465,00			231,00	
Wilcoxon Signed Ranks Test			0,000			0,000

	Group 1			Group 2		
	Before	After 10 days	p	Before	After 10 days	p
Syntoms	12,27±3,94	0,10±3,05		14,03±3,43	1,40±1,85	
Mean Rank		15,50			15,50	
Sum of Ranks		465,00			465,00	
Wilcoxon Signed Ranks Test			0,000			0,000

Additionally the two groups showed significant differences before and after three and ten days of treatment by the two treatment regimens as can be observed in Table 11 by the Wilcoxon Signed Ranks Test following the natural course of the disease.

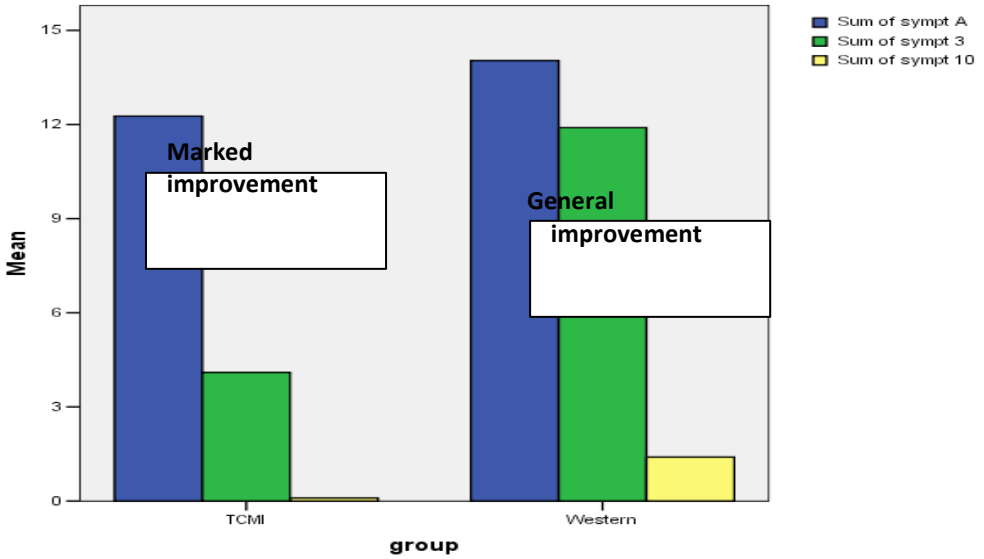

Figure 2 – Mean sum of symptoms before and after 3 and 10 days of treatment in TCM and Western Group

Side effects and secondary complications

There was no registration of any side effects in both groups. However eight patients of Control group and one patient of Experimental one presented secondary complications. The case of secondary complication in the Experimental group was related with an aggravation of a latent gastritis in a *Xiao Chai Hu San* case just in the first consult. The cases of the control group were related with self-wrong-medication or chronic diseases aggravated by ILI condition. Two patients of the control group stop the medication referring bad reaction to the treatment regimen.

The TCM diagnosis and the six channels differentiation process of the 60 cases determine the location, the nature and differentiation of the trends of development and changes in disease. In the sample studied in the peak 2007/2008 influenza's season were diagnosed 11 cases of *Zhong feng* and 17 cases of *Shanghan*, which means that almost half of the cases studied present a simple *Tai Yang* condition (Table 12). The presence of these two patterns is not different in both groups and presented a significant correlation with age (p□0,005). This indicate that the younger patients of

both groups that have a simple *Tai Yang* case have the tendency to have an Excess pattern (*Shanghan*) and the older a Vacuity (*Zhongfeng*) *Tai Yang* pattern. However, the association of variables Age and differentiated patterns was not true for all the other channel's patterns observed in the two groups.

Table 12 – Frequency and Sum of the cases observed for the variable Differentiation Pattern diagnosed in Experimental and Control groups

Six Channells Patterns	Experimental Group	Western Group	Total
Tai Yang *Shanghan*	9	8	17
Tai Yang *Zhongfeng*	6	5	11
Tai Yang concurrent pattern (*Hebing*)	7	7	14
Tai Yang transferred pattern (*Bianzheng*)	4	4	8
Shao Yang	4	4	8
Wenbing	0	2	2
Total	30	30	60

The vacuity and excess patterns of *Tai Yang* were observed in the very first days of the disease and were treated with the treatment method of expel wind and harmonize *Wei Qi* and *Ying Qi* with the classic formula *Gui Zhi tang* in the first case, and by the treatment method of promote sweating and resolve the exterior and regulate the Lung functions with *Ma Huang tang*, in the second case (Table 13). The two prescriptions are used for a very short period of time. Two patients that did not observe these indications showed clear signs of heat and worsening of some ILI related symptoms.

The strength of the pathogenic factor and patient *Zheng Qi* have determined fourteen (14) cases of *Tai Yang* concurrent patterns (*Hebing*) with cases of exterior cold concurrent with internal heat pattern in the Lung and cases of exterior repletion complicated by interior rheum pattern. The first cases occurred mainly in young people with internal heat conditions. For the first condition was applied the treatment method of dissipate wind-cold externally, and internally to clear the depressed heat by the classic formula *Da Qing Long Tang*.

The two cases of water rheum observed in experimental group were patients that have the constitutional tendency to collect water rheum. This condition is aggravated by wind-cold blocking the exterior, damage of the lung functions and congestion of the fluids in its interior. The lung is unable to descend and disperse,

witch results in cough and painting breathing and copious white phlegm. The treatment method applied is, on the exterior to resolve wind-cold and in the interior to eliminate the water rheum with the classic prescription *Xiao Qing Long Wan*.

Eight (8) *Tai Yang* transferred patterns, were also observed, with cases of lung heat panting, cough patterns. The two cases of excess heat obstructing the lungs treated in experimental group are second episodes of ILI, one related with a wrong treatment regimen and the other with a second exposition to wind-cold before complete cure of anterior condition. In these cases there was yellow tongue fur, rapid pulse and perspiration. The method used to treat this condition has been to clear heat and regulate the Lung descendent function with the classic prescription *Ma Huang Xinren Gancao Shigao Tang.*

Table 13 – Frequency and Sum values for the variables Classic TCM Prescriptions and Western Medication in Experimental and Control groups.

Formulas	Experimental Group	Western Group*	Total
Ma Huang San	9	0	9
Gui Zhi San	6	0	6
Xiao Chai Hu San	4	0	4
Da Qing Long San	2	0	2
Ma Huang Xingren Gancao Shigao San	3	0	3
Ge Gen Huang Qin Huang Liang San	2	0	2
Chai hu Gui Zhi San	2	0	2
Western Medication	0	30	30
Total	30	30	60

*The different western medication regimens were registered

From the two cases treated in the experimental group with acute heat watery diarrhea, one was an ILI condition of gastrointestinal type that happened in a Lisbon school and affected teachers and children; the other was a second ILI episode with an incorrect self-medicated method. In the two cases was used the treatment method of clear heat and stop the diarrhea using the classic prescription *Ge Gen Huang Qin Huang Liang Wan*.

In the present study were also observed eight conditions of Shao Yang pattern.

Four were treated in the experimental group by the treatment method of harmonizing and resolving the exterior and interior condition with the governing formula *Xiao Chai Hu Wan*. It is interesting to note that one of the *Shao Yang* cases treated by a western doctor presents an ILI secondary complication, namely, an ear infection and loose of voice which were treated with antibiotic with no results. The gallbladder qi becomes depressed and bond. The depressed qi transformed into fire. The nature of the fire is

to flare upward and its rising dries the orifices and can cause the condition observed. After the experimental period this condition was treated with TCM.

The two cases of *Tai Yang* and *Shao Yang* concurrent patterns were caused by an untreated Tai yang pattern that was aggravated by climate and daily life stress conditions. There was, in both cases, a severe pain in the back, neck and members and distension in the costal region. The treatment method applied was to resolve the exterior, and harmonize with the classic formula *Chai Hu Gui Zhi Wan*.

In this study were also diagnosed two cases of Wind-heat type in group 2 of *Wei Qi* level, followed, with no secondary complications by Western treatment regimen. It was not observed any case of simple *Yang Ming* disease.

CONCLUSIONS

In this study, the six channels principle of pattern identification discussed in the "*Shang Han Lun"* revealed to be a good method and guide for the pattern identification of externally contracted diseases, like ILI, in the Lisbon region of Portugal.

This study pointed out that "*Shang Han Lun"* formulas can: 1) Reduce the recovery period of the disease; 2) Reduce the secondary infections; 3) Avoid the self-medication abuse of antibiotics and anti-inflammatory substances.

This study also indicate that, for TCM intervention, it is decisive, before the increase of temperature higher than 38ºC, to expel the pathogenic factor and prevent the wide and rapid spread of this *Xie Qi* .

The clinical knowledge present in this method need the development and maturation of clinical thought and observation analysis capacities by TCM professionals. It is also important the development of health consciousness of citizens to prevent the disease, be aware of primary manifestations and act appropriately. According to that this study recommends, on one hand, the correct preparation of TCM professionals in "*Shang Han Lun"* clinical methodology and, on other hand, the development of preventive strategies, based on TCM principles and methods.

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