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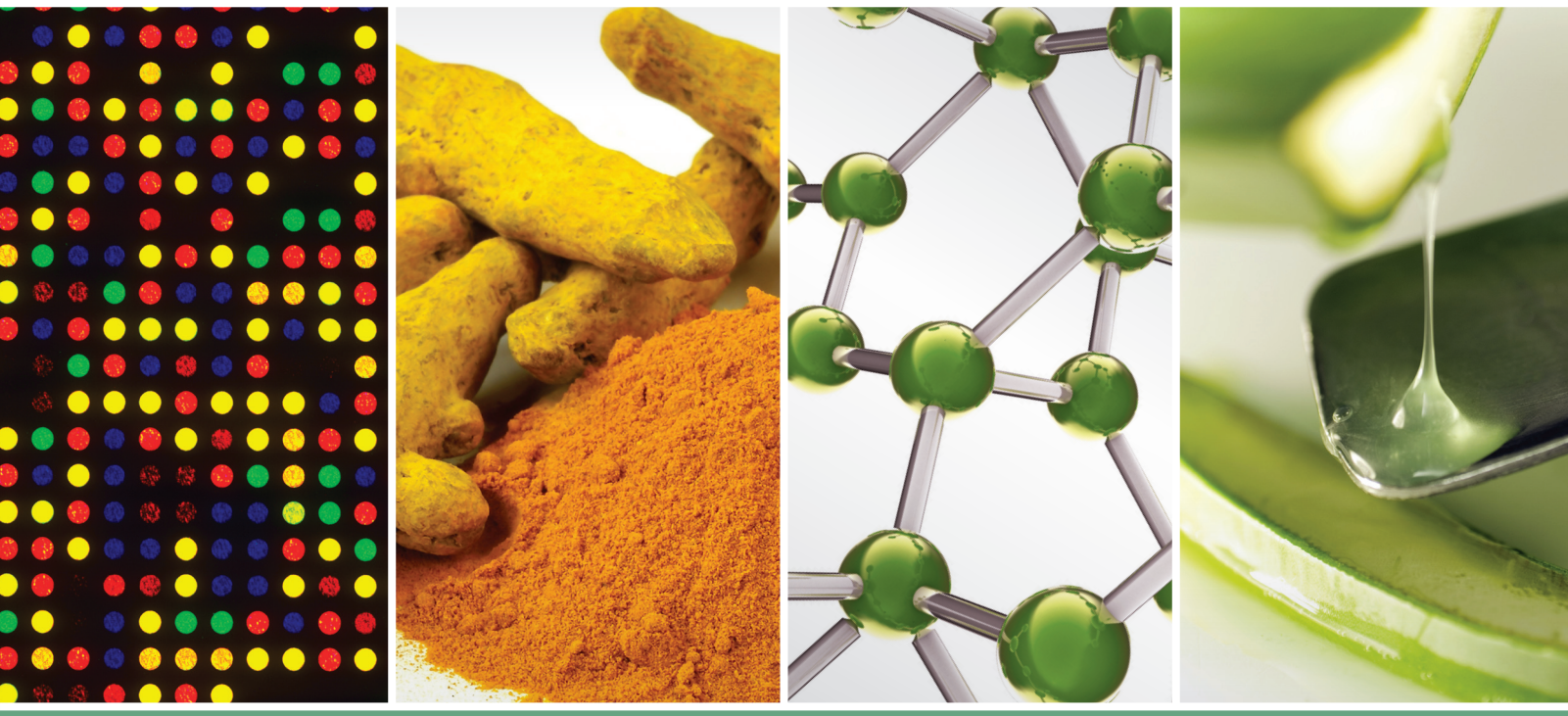
GAP: From Sound Design to Practical Implementation in Clinical Trials for Traditional Chinese Medicine

Guest Editors: Hongcai Shang, Boli Zhang, Zhaoxiang Bian, Youping Li, Mike Clarke, and Nicola Robinson



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Editorial

GAP: From Sound Design to Practical Implementation in Clinical Trials for Traditional Chinese Medicine

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The past few years have witnessed encouraging progress in improving the methodological quality of clinical research of traditional Chinese medicine (TCM). This improvement has contributed to wider academic acceptance of the findings of TCM clinical studies, which were previously deemed dubious. As a proof of this statement, one clinical study testing the effects of a Chinese patent drug Qili Qiangxin Capsules on chronic heart failure has just published a research article on the Journal of the American College of Cardiology, a medical journal of international prestige. However, a sound and scientific design does not always see to its practicality in the conduct of the study, and in fact we observed a widening gap between the two elements. In this special issue, we called for papers discussing efforts to bridge the gap between scientific design and practical implementation of clinical research with TCM.

In Y. Xing et al.'s review article, "*The effects of Wenxin Keli on P-wave dispersion and maintenance of sinus rhythm in patients with paroxysmal atrial fibrillation: a meta-analysis of randomized controlled trials*," they synthesized and assessed the results of randomized controlled trials (RCTs) in order to address a specific clinical question and critically commented on several practical issues in the conduct of TCM clinical research.

In another review article, "*Clinical research of traditional Chinese medicine needs to develop its own system of core outcome sets*," L. Zhang et al. proposed constructing a system of core outcome sets that caters for clinical evaluation of TCM after reviewing existing problems in the choice of outcomes to be assessed in a clinical study.

Patient value is one of the three components necessary for evidence-based clinical decision-making. Patient values and its various manifestations also have a crucial role to play in the conduct of a clinical research and in the evaluation of TCM efficacy and safety. W. Mu and H. Shang called for academic attention to this area of research in their paper entitled "*Understanding patient values and the manifestations in clinical research with traditional Chinese medicine—with practical suggestions for trial design and implementation*."

Issues around compliance control in clinical research of TCM always attract interests. W. Zheng et al. summarized practical barriers to the management of incompliant behaviors from past experiences of being a clinical trial investigator and put up with point-to-point solutions in their review article entitled "*Improving participant adherence in clinical research of traditional Chinese medicine*."

In H. Yu et al.'s research article "*Clinical study on the prevention of oxaliplatin-induced neurotoxicity with Guilongtongluofang: results of a randomized, double-blind, placebo-controlled Trial*," they introduced the measures they took to balance the rigorousness of study design and its practicality and provided a successful example.

In a similar vein, J. Pu et al. explained in the research article "*Chinese medicine Shensongyangxin is effective for patients with bradycardia: results of a randomized, double-blind, placebo-controlled multicenter trial*" their experiences of taking consideration of real clinical circumstances into the process of trial design, so as to narrow the gap between research design and implementation.

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Research Article

Chinese Medicine Shensongyangxin Is Effective for Patients with Bradycardia: Results of a Randomized, Double-Blind, Placebo-Controlled Multicenter Trial

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To evaluate the efficacy and safety of Shensong Yangxin (SSYX) in patients with bradycardia arrhythmias, a randomized, double-blind, and placebo-controlled study was conducted. Patients with bradycardia were randomly assigned to receive either SSYX (trial group, $n = 115$) or placebo (control group, $n = 104$) for 4 weeks. ECG, 24-hour continuous ECG recording, echocardiography, and hepatic and renal function were evaluated at baseline and after treatment. Results showed that the average heart rate, the fastest heart rate, and the lowest heart rate in the trial group were all significantly higher than those in the control group at the end of treatment ($P < 0.05$ or 0.01, resp.). Compared with pretreatment, the average heart rate, the fastest heart rate, and the lowest heart rate in the trial group all increased significantly after treatment ($P < 0.05$ or 0.01, resp.). Both the efficacy and the symptom scores in the trial group were significantly better than those in the control group after treatment (both having $P < 0.01$). No severe adverse effects were reported. In conclusion, SSYX treatment significantly increased the heart rate in patients with bradycardia without severe side effects. The exact mechanisms remain to be further explored.

1. Introduction

Bradycardia is classified as a pulse rate below 60 beats per minute and is a common phenomenon in both healthy and disease conditions [1, 2]. Bradycardia may be a common manifestation of general conduction system disease or iatrogenic, due to medications used for atrial fibrillation rate control [3], which is characterized by a spectrum of arrhythmias including sinus bradycardia, sinus pauses, atrial fibrillation or flutter, and paroxysmal supraventricular tachycardia. The symptoms of bradyarrhythmia are most commonly intermittent syncope or presyncope but may be general and nonspecific. Some patients with sinus node disease are unable to appropriately increase their heart rate with exercise. Others may present with symptoms due to the underlying cause, such as myocardial infarction or drug toxicity.

Bradycardia can include sinus-node dysfunction (sick sinus syndrome) and atrioventricular block [4, 5]. The symptoms are often related to the bradycardia itself, as well as dysfunction of the autonomic nerve system (e.g., dizziness, fatigue, weakness, chest distress, or heart failure). In such cases, treatment targeted solely to correct bradycardia may not be effective in elimination of symptoms [6]. Besides, currently available drugs (e.g., atropine, isoproterenol, and theophylline) used to increase sinus rhythm are not tolerated for long term because of their side effects [7–9]. Since overdrive suppression of sinus automaticity may result in long pauses, syncope often occurs when

tachycardia terminates [10]. Management for bradycardia-tachycardia syndrome is difficult because most antiarrhythmic drugs or the drugs that control the heart rate during tachycardia by blocking atrioventricular conduction such as β-adrenergic receptor blockers, calcium-channel blockers, or digitalis may lead to more severe bradycardia when the tachyarrhythmia terminates. For those patients, a cardiac pacemaker would usually be implanted before drug treatment [11]. Consequently, effective drugs with low side effects are of high interest as alternatives for treating those patients.

Some traditional Chinese medicines have been used to treat the disease related to arrhythmia for thousands of years. Shensongyangxin (SSYX) is a traditional Chinese medicine developed originally for treating cardiac tachyarrhythmias and it is a compound of the traditional Chinese materia medica consisting of 12 ingredients including *Panax ginseng*, dwarf lilyturf tuber, and Nardostachys root. Previous data suggested that SSYX has actions that may be beneficial in the treatment of symptomatic bradycardia. Small clinical studies demonstrated that SSYX effectively reduced ventricular premature beat and prevented bradycardia [12, 13]. Whole cell patch clamping experiments revealed that SSYX was a multiple ion channel blocker [14]. Preliminary studies suggested that SSYX can reduce the number of ventricular ectopic beats while mildly increasing the heart rate [15, 16]. However, extensive clinical trials have not been performed. Therefore, there are not evidence-based data from multicenter studies to confirm the clinical effects of SSYX. In order to further prove the effects of SSYX and cumulate the clinical data, a randomized, double-blind, placebo-controlled clinical study was designed to fully evaluate the efficacy and safety of SSYX in patients experiencing bradycardic arrhythmias.

2. Patients and Methods

2.1. Eligibility and Exclusion Criteria. This study was a randomized, double-blind, placebo-controlled, multicenter study. Patients with the age of 18 to 70 years accompanied by symptomatic bradycardia (average heart rate of 40~60 bpm) were enrolled to the study. However, patients indicated for permanent pacing therapy could be considered for the study only when the patients refused to do so.

Patients who met at least one of the following conditions were eligible: (1) sick-sinus syndrome with: ① average ventricular rate of 40 to 50 bpm; ② average ventricular rate of 50 to 60 bpm with the lowest rate less than 35 bpm accompanied by symptoms related to bradycardia; ③ sinus rhythm or other escape rhythms in atrium, AV junction, or ventricle that occurred ≥2.0 s after the termination of tachyarrhythmia; (2) atrioventricular block (AVB): ① third degree AVB with documented asystole not longer than 2.5 seconds or escaped heart rate not slower than 40 bpm while awake; ② second degree AVB; ③ first degree AVB with prolonged PR interval longer than 300 ms or with symptoms due to loss of atrioventricular synchrony; (3) chronic bifascicular and trifascicular block; (4) bradycardia-tachycardia syndrome.

Exclusion criteria included the following: (1) drug induced bradycardia; (2) endocrine or metabolism abnormalities and electrolyte disequilibrium; (3) acute myocardial infarction or unstable angina pectoris; (4) severe congestive heart failure (NYHA functional class III or IV); (5) uncontrolled hypertension; serious respiratory dysfunction or asthma; (6) liver, renal dysfunction; (7) primary hematopoietic system disease; (8) pregnant or child nursing; (9) allergy to study drugs; (10) patients enrolled to other drug studies; (11) blood pressure less than 90/60 mmHg; (12) bradycardia history shorter than 2 months; (13) syncope due to bradycardia; (14) R-R interval of ≥3.0 seconds; (15) patients who were currently treated with class I, III, or IV antiarrhythmic drugs were also excluded.

The study protocol was fully explained and written informed consent was obtained from each participant. The present study was approved by the Ethics Committee of Cardiovascular Institute and Fu Wai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, and the Ethics Committees of the other 10 hospitals.

2.2. Study Design. This randomized, double-blind, placebo-controlled, multicenter trial was conducted at 11 hospitals across the mainland of China, during October 2007 to July 2008. Patients were randomized using Q-DAS statistical software by random permuted blocks and stratified by centers; the locations were divided into 11 regions, to orally receive either SSYX or placebo 1.6 g tid for 4 weeks. The SSYX capsule and placebo were produced and tested by Yiling Pharmaceutical Corporation (Shijiazhuang, China). They were identical in size, weight, color, and taste. Compliance with the study medication was monitored by counting the capsules individually.

Group assignment for all subjects was determined using a random table prior to the initiation of the study. The sequence of assignments was unknown to any of the investigators. Each assignment was kept in a sealed envelope and the order in numeric number was shown on the outside of the envelope. Thus, the orders could not be changed. Envelopes were arranged in order. The principal investigators generated this random selection a few months before recruiting the first subject. All the evaluations were performed by physicians or nurses who were blinded to the treatment given, using the same set of questionnaires and guidelines.

For all patients, the medical history, physical examination, blood tests (including serum glucose, electrolyte, GPT, GOT, creatinine, and urea nitrogen), 12-lead ECG, 24-hour Holter recording, and echocardiogram were screened. Diagnosis of the bradycardia was confirmed by 24-hour Holter recording. Follow-up clinical visits were scheduled at 4 weeks. All measurements were performed independently by two researchers and the values averaged. For all assays the intraobserver and interobserver variation coefficients were less than 5%, respectively. The participants screening and enrollment flowchart was shown in Figure 1.

The minimum sample size required for the study was calculated by the following. Compared with placebo, the experimental medicine curative effect is about 60%, control

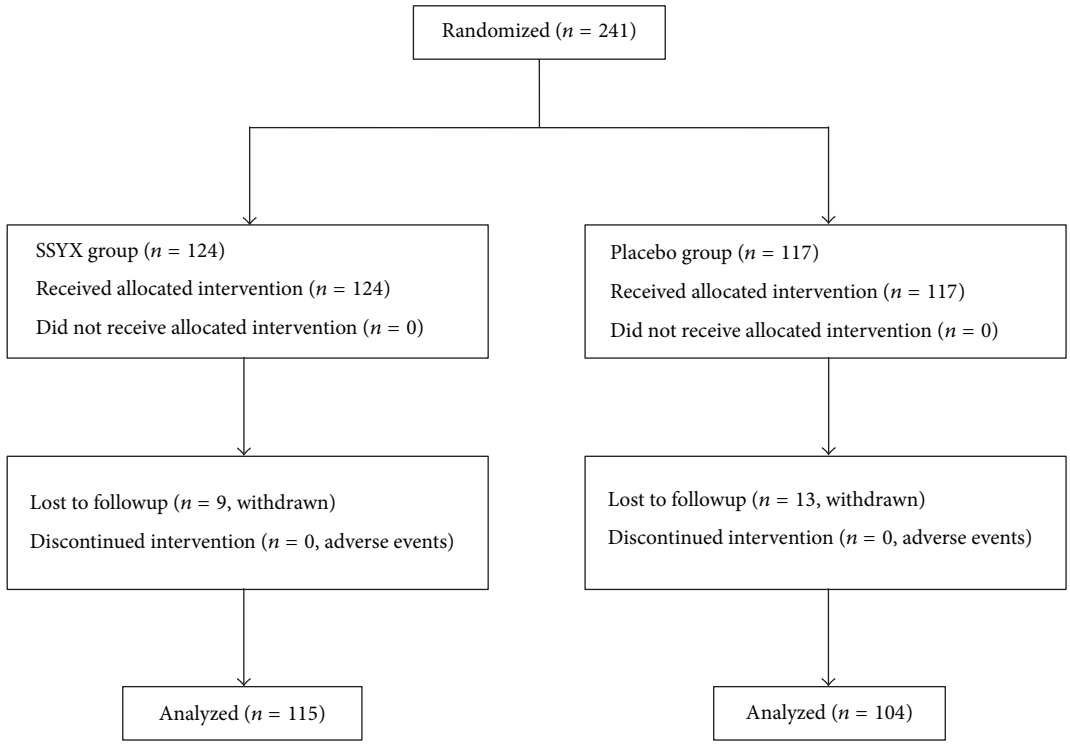

Figure 1: Participants screening and enrollment flowchart.

medicine is about 40%, alpha is 0.05, and beta is 0.2 (study power 80%), estimate for 98 cases in each group. Considering the drop factors, the study was designed to enroll 280 cases (140 cases in the trial group and 140 cases in the control group).

2.3. Outcome Measures. The primary outcome was objective criterion obtained by 24-hour Holter recording and the secondary outcome was subjective criterion obtained by symptom scores.

The criteria for assessing the therapeutic effects of SSYX capsules were formulated according to the "Guiding Principles of Clinical Research on Treatment of Coronary Heart Disease with Traditional Chinese New Drugs" published in 2002 [9] and the "Therapeutic Effects and ECG Evaluation Criteria for Treatment of Coronary Heart Disease" published in the Symposium for Coronary Heart Disease and Arrhythmia with integrated TCM and Western Medicine in 1998 [17].

The objective criteria for assessing the therapeutic effects of SSYX capsules on bradycardia were as follows according to the results obtained by 24-hour Holter recording. (1) A markedly effective response was defined as an increase of 20% or more in the average heart rate. (2) An effective response was defined as an increase from 10% to 20% in the average heart rate. (3) No effective response was defined as less than 10% increase or even decrease in the average heart rate.

The criteria for the symptom score depended on the frequency and degree of the symptoms which included palpitation, shortness of breath, fatigue, chest distress, agrypnia, and night sweat. (1) A markedly effective response was defined as the symptom scores decreased by >70%. (2) An effective response required a decrease from 30% to 70% in the symptom scores. (3) No effective response was defined as less than 30% decrease in the symptom scores.

2.4. Safety Monitoring. All patients underwent follow-up office visits weekly during therapy. At each follow-up, blood routine, transaminases, serum urine nitrogen (BUN), physical examination, echocardiography, and 12-lead ECG were measured and the incidence and severity of various side effects (i.e., nausea, vomiting, diarrhea, abdominal pain, headache, and dizziness) which may be associated with therapy were monitored.

2.5. Statistical Analysis. Continuous variables are given as mean ±SD. Comparison of the basic characteristics between the control group and the trial group was made using Student t-test. As the data were normally distributed, the difference between the two groups in terms of the changes of Holter recording before and after treatment was analyzed by repeated measures ANOVA. Pearson Chi-Square test or Fisher's exact test was used to compare categorical variables.

Calculations were performed with the statistical software SAS 9.1.3 (SAS Institute Inc., USA) and Q-DAS for Clinical Trial 3.0. (Q-DAS software technology, China). The SAS data sheets ITT (intention-to-treat was defined as patients who were treated at least once) and FAS (full analysis set was defined as the participants including eligible cases and drop-out cases) were used for efficacy and SS (safety set was defined

Table 1: Basic characteristics of study population.

Groups	Trial group (n = 115)	Control group (n = 104)
Gender M/F (n)	60/55	47/57
Height (cm)	165.68 ± 7.85	165.15 ± 7.71
Weight (kg)	66.69 ± 10.24	65.35 ± 9.99
Systolic blood pressure (mmHg)	126.64 ± 13.64	128.26 ± 13.70
Diastolic blood pressure (mmHg)	77.84 ± 7.71	76.51 ± 8.33
Heart rate (bpm)	54.09 ± 5.87	53.13 ± 5.79
QT interval (ms)	430.42 ± 35.85	437.07 ± 34.32
Left ventricular ejection fraction (%)	65.88 ± 6.68	65.28 ± 8.04
Left ventricular end diastolic dimension (mm)	49.70 ± 6.50	48.63 ± 5.57
NYHA class, n (%)		
I	95 (82.6)	86 (82.7)
II	20 (17.4)	18 (17.3)
Hypertension, n (%)	37 (32.2)	32 (30.8)
Ischemic heart disease, n (%)	32 (27.8)	39 (37.5)
Diabetes mellitus n (%)	6 (5.2)	7 (6.7)
History of bradycardia n (%)	13 (11.3)	7 (6.7)
Types of bradycardia (%)		
Sinus bradycardia, sinus pauses	64 (55.7)	65 (62.5)
Atrioventricular block	11 (9.6)	8 (7.7)
Bradycardia-tachycardia syndrome	40 (34.8)	31 (29.8)

Table 2: Heart rate in the trial group and the control group at baseline and 4 weeks.

HR variables	Trial group	Control group	P value
AHR (bpm)			
Baseline	53.38 ± 5.16	53.83 ± 4.17	0.482
4 weeks	60.50 ± 8.70*	56.50 ± 5.99*	0.000
FHR (bpm)			
Baseline	95.50 ± 24.94	95.31 ± 20.64	0.952
4 weeks	105.54 ± 24.97#	98.93 ± 18.85	0.029
LHR (bpm)			
Baseline	33.50 ± 3.62	33.98 ± 3.91	0.350
4 weeks	40.74 ± 7.67#	38.08 ± 5.85#	0.005

HR: heart rate; AHR: average heart rate; FHR: fastest heart rate (bpm); LHR: lowest heart rate.
At baseline, there are 115 patients in the trial group and 104 patients in the control group. At the end of 4 weeks, 1 patient in the trial group and 4 patients in the control group refused to repeat 24-hour Holter, so their HR variables are missed.
*$P < 0.05$ versus pretreatment in the same group.
#$P < 0.01$ versus pretreatment in the same group.

as participants who received treatment and safety analysis at least once).

3. Results

3.1. Patient Characteristics. From October 2007 to July 2008, 241 consecutive patients were enrolled in this prospective study from 11 hospitals across the mainland of China. Of the 241 patients enrolled, 124 patients were randomized to the trial group and 117 patients to the control group. Nine patients in the trial group and 13 patients in the control groups were lost to follow up. As a result, a total of 219 patients (115 in the trial group and 104 in the control group) completed the study. The main patient characteristics and the types of bradycardia were summarized in Table 1. The arms of the study were well balanced with respect to age, gender, height, weight, blood pressure, average heart rate (AHR), fastest heart rate (FHR), lowest heart rate (LHR), left ventricular ejection fraction, QT interval, NYHA class, ischemic heart disease, history of bradycardia, sinus bradycardia, sinus pauses, atrioventricular block, and bradycardia-tachycardia.

3.2. Changes of Heart Rate. One patient in SSYX group and 4 patients in placebo group refused to repeat 24-hour Holter recording at the end of treatment.

As shown in Table 2, the average heart rate in the trial group was significantly higher than that in the control group after treatment (60.50 ± 8.70 versus 56.50 ± 5.99, $P < 0.01$). As for the effect of SSYX on heart rate, we found that the 24-hour average heart rate increased by 7.15 ± 7.43 in the trial group and by 2.60 ± 4.53 in the control group after treatment ($P < 0.01$). Both the fastest heart rate and the lowest heart rate in the trial group were significantly higher than those in the control group at the end of 4 weeks ($P < 0.05$ or 0.01, resp.). Compared with pretreatment, the average heart rate, the fastest heart rate, and the lowest heart rate in the trial group all increased significantly after treatment ($P < 0.05$ or 0.01, resp.). The average heart rate and the lowest heart rate in the control group were also increased significantly at the end of 4 weeks ($P < 0.05$ or 0.01, resp.), whereas the fastest heart rate did not change significantly ($P > 0.05$).

Table 3: The objective efficacy comparison between the trial group and the control group.

Group	n	MER (%)	ER (%)	NER (%)	P value
Trial group	124	30 (24.2)	43 (34.7)	51 (41.1)	0.000
Control group	117	1 (0.9)	22 (18.8)	94 (80.3)	

MER: markedly effective response; ER: effective response; NER: no effective response.

Table 4: The symptom scores analysis between the trial group and the control group.

Time	Trial group ($n = 115$)	Control group ($n = 104$)	P value
0 week	7.66 ± 3.95	7.35 ± 3.79	0.547
4 weeks	3.42 ± 2.88	4.97 ± 3.26	0.000

3.3. Objective Efficacy. The results of objective efficacy were analyzed in all of the participants including eligible cases and drop-out cases. As shown in Table 3, the markedly effective response rate was 24.2% in the trial group and 0.9% in the control group after treatment. The effective response rates were 34.7% in the trial group and 18.8% in the control group, respectively. Significant differences were found between the two groups ($P < 0.01$).

3.4. Symptom Scores. The results of symptom scores were shown in Table 4. Compared with the baseline level, the symptom scores in both groups decreased after treatment (3.42 ± 2.88% versus 7.66 ± 3.95 in the trial group and 4.97 ± 3.26% versus 7.35 ± 3.79 in the control group). Compared with the control group, the symptom score in the trial group was significantly lower ($P < 0.01$).

3.5. Adverse Events. Adverse events most possibly related to the treatment were reported in 1 (0.8%) patient in the trial group and 5 (4.3%) patients in the control group. Palpitation, headache, stomachache, and abdominal distension were the major symptoms. The symptoms completely recovered a few days after termination of the treatment. Neither death nor serious adverse event was reported during the study.

4. Discussion

The current study was designed to evaluate the efficacy and safety of SSYX in the treatment of patients with bradycardic arrhythmias. The results demonstrated that SSYX treatment significantly increased heart rate in patients with bradycardia. The total effective rate was 63.5% in the trial group and 22.1% in the control group. Symptom scores were also significantly improved in the trial group compared with the control group. These results compare well with studies that suggested that SSYX has effect on paroxysmal atrial fibrillation [18] and premature ventricular contractions [19].

The effects of SSYX in treating cardiac rate and contraction abnormalities may be conferred by such ingredients of SSYX as *Panax ginseng*, which may balance the tension of autonomic nerve system [20]. Our previous electrophysiological study demonstrated that SSYX increased heart rate and enhanced conducting capacity of the heart in the Chinese miniature swine only when the autonomic nervous system was intact [21]. Another research has shown that SSYX affects cardiac action potentials by lowering the L type calcium channel currents and transient outward potassium currents in rabbit pulmonary vein myocytes [22], while a study on guinea pig ventricular myocytes showed that these channels were blocked [16] and another study found that SSYX could block these and many other ion channels such as the sodium current, the inward rectifier potassium current, and the delayed rectifier current, in rat and guinea pig ventricular myocytes [14].

It is earlier to come to a conclusion on the effect of SSYX on patients with II (type 2) or III degrees of atrioventricular block because of the small number of patients tested. For the sake of safety, patients with extreme bradycardia (e.g., heart rate below 40 beats per minute while awake, R-R interval exceeding 3.0 seconds in sinus rhythm, or experiencing syncope probably caused by bradycardia) were excluded in the trial. For those patients, implantation of a pacemaker is recommended if necessary.

There was no death or severe adverse events registered during the study. No significant changes in hepatic and renal function have been observed immediately after study. Neither proarrhythmic events nor QTc prolongation related to SSYX treatment were recorded. The most common adverse effects were temporary stomachache and abdominal distension. The outcomes of the study suggested that clinical use of SSYX was safe and effective for treating patients with sinus bradycardia.

There are some limitations in our study. First, the observation time is only 4 weeks and hence a longterm study is obviously needed to further confirm our results. Second, clinical and laboratory findings were used as the endpoints in our study, whereas a hard clinical endpoint such as mortality should be used in a large sample of patients in a future study. Third, a positive control is not set in this study and we will evaluate if SSYX is optimal efficiency or noninferiority in the future.

In conclusion, this study shows that SSYX is safe and effective for the treatment of bradycardia. This result means that SSYX should be considered an alternative treatment for bradycardic patients, especially those who are not recommended for pacemakers or patients who choose not to have a pacemaker fitted.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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References

[1] R. G. Holly, J. D. Shaffrath, and E. A. Amsterdam, "Electrocardiographic alterations associated with the hearts of athletes," *Sports Medicine*, vol. 25, no. 3, pp. 139–148, 1998.

[2] W. J. Groh, "Arrhythmias in the muscular dystrophies," *Heart Rhythm*, vol. 9, no. 11, pp. 1890–1895, 2012.

[3] L. Feng, J. Gong, Z.-Y. Jin et al., "Electrophysiological effects of Chinese medicine Shen song Yang xin (SSYX) on Chinese miniature swine heart and isolated guinea pig ventricular myocytes," *Chinese Medical Journal*, vol. 122, no. 13, pp. 1539–1543, 2009.

[4] D. Durham and L. I. Worthley, "Cardiac arrhythmias: diagnosis and management. The bradycardias," *Critical Care and Resuscitation*, vol. 4, no. 1, pp. 54–60, 2002.

[5] J. W. Ufberg and J. S. Clark, "Bradydysrhythmias and atrioventricular conduction blocks," *Emergency Medicine Clinics of North America*, vol. 24, no. 1, pp. 1–9, 2006.

[6] W. J. Brady Jr. and R. A. Harrigan, "Diagnosis and management of bradycardia and atrioventricular block associated with acute coronary ischemia," *Emergency Medicine Clinics of North America*, vol. 19, no. 2, pp. 371–384, 2001.

[7] G. Das, "Cardiac effects of atropine in man: an update," *International Journal of Clinical Pharmacology Therapy and Toxicology*, vol. 27, no. 10, pp. 473–477, 1989.

[8] L. Hendeles, M. Weinberger, G. Milavetz, M. Hill III, and L. Vaughan, "Food-induced "dose-dumping" from a once-a-day theophylline product as a cause of theophylline toxicity," *Chest*, vol. 87, no. 6, pp. 758–765, 1985.

[9] D. P. Zipes, A. J. Camm, M. Borggrefe et al., "ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines," *Journal of the American College of Cardiology*, vol. 48, no. 5, pp. e247–e346, 2006.

[10] W. S. Aronow, "Management of atrial fibrillation in the elderly," *Minerva Medica*, vol. 100, no. 1, pp. 3–24, 2009.

[11] P. Rucinski, A. Rubaj, and A. Kutarski, "Pharmacotherapy changes following pacemaker implantation in patients with bradycardia-tachycardia syndrome," *Expert Opinion on Pharmacotherapy*, vol. 7, no. 16, pp. 2203–2213, 2006.

[12] J. Z. Huang, H. Yan, X.G. Chen, and J. C. Liang, "Effect of Shensong Yangxin Capsule on ventricular premature beat and heart rate variablity," *Modern Medicine and Health*, vol. 22, no. 18, pp. 2843–2843, 2006.

[13] X. X. Shen and W.X. Lu, "Effect of Shensong Yangxin Capsule on sinus node bradycardi," *Chinese Journal of Information on TCM*, vol. 15, article 76, 2008.

[14] N. Li, K.-J. Ma, X.-F. Wu, Q. Sun, Y.-H. Zhang, and J.-L. Pu, "Effects of Chinese herbs on multiple ion channels in isolated ventricular myocytes," *Chinese Medical Journal*, vol. 120, no. 12, pp. 1068–1074, 2007.

[15] S. Chai, S. Wang, L. Yao, A. Wu, Y. Liu, and C. Rao, "Effect of shensongyangxin capsule on myocardial remodeling and ventricular fibrillation threshold value in rat with coronary artery ligation," *Zhongguo Zhongyao Zazhi*, vol. 34, no. 16, pp. 2101–2104, 2009.

[16] N. Li, Y.-P. Huo, K.-J. Ma, Q. Sun, and J.-J. Pu, "Effects of solution of dry powder of ShenSongYangXin capsule on sodium current and L-type calcium current in ventricular myocytes: experiment with guinea pig," *National Medical Journal of China*, vol. 87, no. 14, pp. 995–998, 2007.

[17] K. J. Chen, J. Z. Liao, and Z. X. Xiao, *Research on Cardiocerebrovascular Diseases*, Shanghai Publishing Company of Science and Technology, Shanghai, China, 1998.

[18] A.-H. Wang, J.-L. Pu, X.-Y. Qi et al., "Evaluation of shensongyangxin capsules in the treatment of paroxysmal atrial fibrillation: a randomized, double-blind and controlled multicenter trial," *Zhonghua yi Xue Za Zhi*, vol. 91, no. 24, pp. 1677–1681, 2011.

[19] J.-G. Zou, J. Zhang, Z.-H. Jia, and K.-J. Cao, "Evaluation of the traditional chinese medicine shensongyangxin capsule on treating premature ventricular contractions: a randomized, double-blind, controlled multicenter trial," *Chinese Medical Journal*, vol. 124, no. 1, pp. 76–83, 2011.

[20] A. Zheng and T. Moritani, "Effect of the combination of ginseng, oriental bezoar and glycyrrhiza on autonomic nervous activity and immune system under mental arithmetic stress," *Journal of Nutritional Science and Vitaminology*, vol. 54, no. 3, pp. 244–249, 2008.

[21] V. Essebag, T. Hadjis, R. W. Platt, and L. Pilote, "Amiodarone and the risk of bradyarrhythmia requiring permanent pacemaker in elderly patients with atrial fibrillation and prior myocardial infarction," *Journal of the American College of Cardiology*, vol. 41, no. 2, pp. 249–254, 2003.

[22] L. Shi, X.-C. Yang, X.-L. Liu, M. Zong, and Y.-L. Wu, "Effects of ShenSongYangXin on action potential and some current channels in isolated rabbit pulmonary vein cardiomyocytes," *Zhonghua yi Xue Za Zhi*, vol. 89, no. 30, pp. 2142–2146, 2009.

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Review Article

Improving Participant Adherence in Clinical Research of Traditional Chinese Medicine

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Ensuring good participant adherence in clinical trials plays an important role in that poor adherence may jeopardize the internal validity of the trial. Improving adherence in clinical trials on traditional Chinese medicine (TCM) has long been a concern for Chinese researchers who are conducting clinical trials. Drawing on from our past experiences in managing patient adherence in large-scale clinical trials, we identified factors that influence adherence and categorized them by sources into factors with respect to the trial protocol, on the part of the patients and the investigators. On this basis, we developed a series of ways to improve participants' adherence, while taking into account the characteristics of TCM trials, in the hope of providing reference for peer clinical researchers.

1. Introduction

Participants' adherence can be defined to describe the implementation of prescribed medical orders in clinical trials. It refers to the subjects' acceptance of prescribed treatment which contained the dosages and courses and followup. Adherence is closely related to the quality of clinical trials; low patient adherence with prescribed treatments is a very common problem in clinical trials and can seriously distort the generalizability and validity of controlled clinical trials [1]. A research showed that different adherence can lead to difference of end events significantly [2]. In addition, it can also save funding and reduce cycle time when improving the adherence in clinical trials.

The adherence in clinical trials had been drawing more and more attentions of researchers abroad in the 1990s, and "The Journal of Compliance in Health Care" pays special attention to it. The phenomenon of non adherence is widespread among clinical trials [1, 3]. A study involved 1367 participants with hypertension showed that there are only 15.9% high adherers [4]. Some patients take medicine by an act of volition, and in double-blind, placebo-controlled trials, the code that was broken can lead to poor adherence also [5].

Poor adherence includes two aspects: one is adherence of drug therapy; that is, the patients fail to take drug in accordance with the prescribed methods of taking medicine, or accept the forbidden treatment, another one is adherence with followup; that is, patients do not follow up or get check on schedule or drop out without any reason during the trial.

For the particularity of TCM clinical trials, there are some characteristic in patients adherence; part of the western medicine doctors mistrust the curative effect of TCM; their negative attitudes toward the TCM trials can lead to the poor adherence. The long course of treatment for the chronic disease can impact the adherence, and some other factors such as the mega dose of TCM, take medicine frequently, the unpalatable of decoction also can hinder adherence. Moreover, it is difficult to produce Chinese medicine placebo, so in a long-term test, once the placebo is recognized, adherence of drug therapy will be influenced.

On the other hand, compared with Western medicine, there are less ADR and invasive test in TCM, and it can improve the adherence to some extent.

Through the implementation of large-scale multicenter clinical trial of TCM—"Qi Shen Yi Qi dropping pill for

myocardial infarction's secondary prevention study" (MISPS-TCM) successfully, the nonadherence was observed from the main performance: some patients can not follow up or take medicine on time; some patients refused to return the surplus medicine for various reasons; some participants refused to continue to take drugs once any adverse event appeared, regardless of whether it was related to the drug or not; Some patients were lost for followup at some stages of the trial with unknown cause [6].

Through the MISPS-TCM, we established a quality management system of clinical trial. Improving the patients adherence is part of the system. According to the project implementation, we will have a discussion about the methods to improve patient's adherence.

2. Factors Related to Participant Adherence in Clinical Trials of TCM

There are many factors which can influence the subjects adherence, among the hypertensive patients with poor adherence, the factors contained forget, discontinue taking the antihypertensive medications as blood pressure has been controlled, unwilling to take medicine at all, fear of adverse reactions, control blood pressure by other ways, the cost, and so on [7]. Another study showed that [8] the poor taste of herbs, troublesomeness of boiling, and worrying about the quality of medicines also are factors of poor adherence.

Studies suggested that the adherence of long-term patients is lower than short-term [9] and adherence of patients with acute disease is better than chronic disease. And the adherence will markedly reduce after subjects have received six months treatment [10–12].

In the MISPS-TCM, there were 467 discontinuations, which can be known as a form of non-adherence. The discontinuations contained 142 for disobedience (30.41%), 130 drops with unknown reasons (27.84%), 82 for adverse events (17.56%), 58 for lack of efficacy (12.42%), 3 for the usage of the forbidden drugs (0.64%), and 52 for other reasons (11.13%). For the main purpose of the trial, we did not focused on the determinants of patient adherence; thus, there have been no more detailed data to analyse the factors. But the staff of MISPS-TCM gathered some experiences. They found that the adherence of patients will be higher under the care of nurses, while the outpatient will perform worse for some reasons such as forget, boredom of taking medicine, ignore the diseases, the disease is controlled temporarily, fear of the ADR, and distrust the medicine (Table 1).

In addition, other factors included the subjects' gender, age, occupation, marital status, education, income, disease types, race, religion, socioeconomic status, instructions about how to take medicine, course of the treatment, the severity of disease, cost and adverse reactions, anxiety of subjects, fear of life quality, social support (comes from family and friends), and experience and self-management ability.

Through the implementation of MISPS-TCM project, the team thought there are three factors that influence the adherence of subjects that mainly comes from the study protocol, the researchers, and the subjects itself.

Table 1: Table of factors related to participant compliance.

1	Forget
2	State of illness is controlled
3	Long course of treatment
4	High cost
5	Unblinding
6	Unwillingness of taking medicine
7	ADR
8	Complexity of instruction for taking medicine
9	Lack of correct understanding to disease
10	Lack of correct understanding to risk return
11	Ignore the disease
12	Low work satisfaction of doctor
13	Important event
14	Psychogeny
15	Improper follow-up plan
16	Difficulty in taking medicine
17	Unsure about treatment
18	Bad doctor-patient relationship
19	Difficult to care for some patients (the disabled, schizophrenic, et al.)
20	Asymptomatic disease
21	Complex description for medication
22	Difficult to get the medicine
23	Not familiar with the drug price
24	No reason

2.1. Study Protocol. (1) The protocol presents complexity, taking medicine frequently, and large dose. In TCM clinical trials, patients were requested to take medicine in large dose and frequently for the small drug loadings. It is difficult for some subjects to accept that (2) the followup frequently influences the daily life and work; (3) more invasive tests (such as blood tests, gastroscopy, etc.) are difficult for subjects to accept; (4) subjects had mental fatigue when they take part in long time trials of TCM; (5) due to the particular character of TCM, the placebo of Chinese medicine can be discriminated easily because of the appearance and smell, and this can make the patient have poor adherence; (6) taste of part of Chinese medicine is terrible, and it is difficult to endure; (7) they have more adverse reactions.

2.2. The Researchers. (1) Researchers are unfamiliar with the protocol of study, and not sufficiently informed subjects about all responsibilities; (2) there is bad or indifferent attitude of researchers; (3) they cannot answer questions for patients satisfactory in time and be distrusted; (4) they cannot handle the issue properly when they meet with adverse events; (5) they are too busy to receive the visitor in time; (6) communication disorders between the doctor and patients for lack of communication skills or use of too much professional terms; (7) they transform the workers frequently.

2.3. The Subjects. (1) The understanding of disease is not enough and does not attach importance to the clinical research; (2) they mistrust the researchers or not satisfied with the researchers' attitude; (3) they are not satisfied with curative effect of the test drug; (4) they have fear of other problems followed with ADR; (5) they have poor memory and cannot take medicine or visit on time. (6) they take part in the trial just for gain the physical examination or free medicine. (7) there have a long distance between address of patient and hospital, and the traffic is inconvenient. (8) they are busy at work; (9) they think do not have to take medicine as the symptoms have disappeared; (10) they are influenced by others around subjects who are negative; (11) the patients are introverted, and shy away from interaction.

3. Measures to Improve Adherence

For the above factors, relevant measures should be taken during enrollment and treatment to improve adherence.

Currently, there are more approaches and strategies on adherence, for example, giving placebo during enrollment, considering study design and conduct from the perspective of participants, and promoting patients' understanding and support to research.

Based on our experiences from MISPS-TCM, measures will be summarized and discussed as follows.

3.1. Prevention Approaches before Enrollment. The prevention approaches before enrollment mainly focus on the study protocol and researchers.

3.1.1. Study Protocol. Study protocol should emphasize the practicability. A good top-level design is half of success. Based on meeting trial demands, clinic visits and outcome measurements should be reduced. Endpoints were selected as outcomes such as a composite of cardiovascular death and nonfatal reinfarction and nonfatal stroke and the events of revascularization in MISPS-TCM, which avoided affecting daily work and life of subjects to a great extent.

In addition, when designing the trial, placebo in precursor can be taken in long term trials to exclude potential subjects with poor adherence [13].

3.1.2. The Researchers. When study protocol is relatively fixed, the key points to improve adherence after enrollment is that the researchers inform subjects sufficiently and are willing to participate the study. In MISPS-TCM, before signing informed consent form, investigators made appointment with subjects and the conversation focused on the following issues: (1) further understanding potential subjects' medical history and determining whether it meet the inclusion and exclusion criteria, (2) explaining them the informed consent form in detail to ensure them voluntary participation, (3) knowing some information about subjects such as their education and family to confirm whether they have high adherence and can participate in the trial throughout.

In the progress of obtaining consent from subjects, attention should be paid to the following points. (1) Get subjects' trust. (2) Researchers who explain information on informed consent to subjects should have better ability of communication and skills and provide relevant information easy to understand and answer queries with good attitude. What is more, researchers should clearly tell subjects how to cooperate. Then subjects determine whether they can offer dedication in research. (3) Time to consider on participation should be enough. A readable "Patient information table" can be provided, which is helpful for potential subjects to discuss. Thereby the condition that subjects are enrolled due to thoughtless consideration can be avoided. (4) Explain the possible risks or inconvenience such as side effects or follow-up visit. It may increase the difficulty of recruitment; however, it can enhance adherence after enrollment owing to nonadherent subjects part who want to get paid. (5) It should be specified that all therapies possibly have side effects. Potential adverse reactions of treatment as well as controlled drugs should be informed ahead of time. Once adverse events occur, subjects can keep contact with research staff at any time.

3.2. Measures to Improve Adherence after Enrollment. After participants sign informed consent form and are enrolled, researchers are recommended to strengthen communication with participants and guide them to rational drug use. Furthermore, with the help of research management office, participants should be offered a variety of convenient conditions if possible to avoid poor adherence. Relevant measures are addressed as Figure 1.

3.2.1. Regular Reminding

(a) Card for Medication, and Follow-Up Plans. In MISPS-TCM, the card for reminding was placed in medicine box, including time, dose of medication, and visit. The card can be presented as a calendar, which was convenient for their family to see relevant information and provide assist.

(b) Giving Out Drugs. In MISPS-TCM, drugs were distributed to subjects according to how much would be taken in one follow-up period, and they were informed with the next clinic visit was informed. Drugs needed in the whole research should not be once given to subjects.

(c) Sending Message or Telephone Call [14, 15]. Researchers send message or telephone call on time of medications and clinic visit and request participants to provide feedback on time. Different contents can be sent to subjects. For the younger, the words can be lively and relaxing, and a joke or health tip can be added, while for the older, simple and kind message is appropriate instead of too professional expressions.

3.2.2. Publicity and Education. The patient handbook was prepared in MISPS-TCM, and each participant can get one. Information related to this study was included such as secondary prevention of myocardial infarction, objective, method, composition of Chinese herbal medicine, and benefits and risks of participating in this trial. Thereby participants

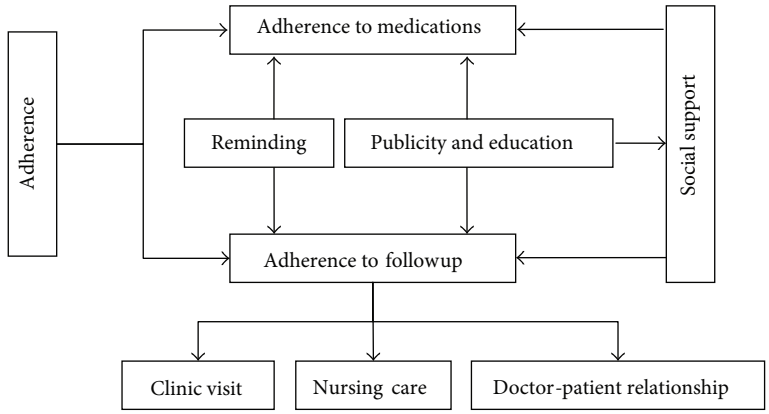

Figure 1: Measures to improve adherence after enrollment.

were able to fully understand issues associated with disease and our study. It is essential to further improve the subjects' adherence.

Family support for the adherence of patients plays an important role [16], so family and friends can be also involved in education and training on health care and clinical trials when necessary. Then they can have a correct knowledge of disease and trials.

Spreading knowledge of health care and research and emphasizing the importance of prescribed medications and followup will promote participant adherence. Also, it can form a better basis for future research.

Additionally, drugs not allowed to be taken during the trial can be listed in a card, to conveniently remind participants at any time.

3.2.3. Social Support and Community Education [17]. Studies can involve family of participants and community, if possible, and make them realize the importance of adherence to researchers by adherence education. With the help of them, participants can be reminded to take medicine and visit on time. Understanding of family can also increase the confidence to complete the whole research.

3.2.4. Follow-Up Plan. On the basis of following the study protocol, follow-up plan should depend on specific situation of participants such as avoiding the holiday or the inconvenient day. When the visit is over, researchers should remind patients of the next appointment time. For several absent participants, researchers should do telephone interviews in time and ask the reason.

3.2.5. Relevant Service. Investigators and research management office provide convenience for participants during the duration of treatment and followup, for instance, offering traffic allowance, baby-sitting, or free parking and reducing waiting times. The reception room should be kept quiet and clean, and the temperature should be kept pleasant. Coffee, tea, magazines, newspapers, and television are available in this room.

Appropriate health-related information and concerns about their life not only can promote trust but can also confirm whether participants keep healthy.

3.2.6. Doctor-Patient Relationship. Investigators and participants should increase open communication and trust each other. It has several benefits, including that (i) participants can get more information associated with health care in visits; (ii) when patients feel respected, they are willing to discuss some solutions with researchers; (iii) it is convenient to encourage participants to focus on disease changes or some possible adverse events. Also, the problems from participants should be handled in time, thereby removing the gap between doctors and patient. It makes sense to improve adherence.

Participants can contact the researchers by telephone or email to keep communication. It is necessary to assign the research staff responsible for follow-up visits of participants. The following situations must be avoided such as when researchers are busy with daily work, or the preset appointments are replaced, which will emerge as a great barrier to good communication and negotiation between participants and researchers.

3.2.7. Other Measures. Providing rewards or compensation in several forms is also an effective measure including oral incentives, advising appropriate holiday, and providing transportation fee. Compensation should depend on trials itself and economic level in region where clinical trials are conducted. Moreover, sufficient attention should be paid to the principals that the reliability of trials is not changed as a result of compensation. Too low pay will affect the progress of enrollment to some extent, while too high can cause a false positive error.

Additionally, it is necessary to take reasonable solutions when poor adherence occurs in clinical trials. The concept of primary, secondary, and tertiary prevention approaches [18] has provided a good example for researchers committed to clinical trials of TCM.

4. Conclusion

Enhancing participant adherence is a crucial point and is also the emphasis and difficulty in clinical trials. When conducting clinical trials of TCM, appropriate adherence measures should be taken based on practically different situations. For instance, participants and investigators generally have high adherence in primary hospitals, so text message need not be sent. Additionally, cost and efficiency should be taken into consideration.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Wenke Zheng and Bai Chang contributed equally to this paper.

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References

[1] R. B. Haynes and R. Dantes, "Patient compliance and the conduct and interpretation of therapeutic trials," *Controlled Clinical Trials*, vol. 8, no. 1, pp. 12–19, 1987.

[2] L. L. Shang, "Analysis the impact of different treatment adherence on cardiovascular events for patients with Hypertension," *China Practical Medicine*, vol. 8, no. 27, pp. 90–91, 2013.

[3] M. A. Chesney, "Factors affecting adherence to antiretroviral therapy," *Clinical Infectious Diseases*, vol. 30, supplement 2, pp. S171–S176, 2000.

[4] D. E. Morisky, A. Ang, M. Krousel-Wood, and H. J. Ward, "Predictive validity of a medication adherence measure in an outpatient setting," *Journal of Clinical Hypertension*, vol. 10, no. 5, pp. 348–354, 2008.

[5] C. L. Besch, "Compliance in clinical trials," *AIDS*, vol. 9, no. 1, pp. 1–10, 1995.

[6] H. B. Cao, H. C. Shang, B. L. Zhang et al., "Monitoring in clinical trials with multicenter and large sample," *Chinese Journal of New Drugs*, vol. 16, no. 18, pp. 1429–1431, 2007.

[7] B. M. Egan, D. T. Lackland, and N. E. Cutler, "Awareness, knowledge, and attitudes of older americans about high blood pressure: implications for health care policy, education, and research," *Archives of Internal Medicine*, vol. 163, no. 6, pp. 681–687, 2003.

[8] G. L. Ye, "Analysis the outpatients compliance of taking medicine decoction," *Journal of Guiyang College of Traditional Chinese Medicine*, vol. 35, no. 4, pp. 164–166, 2013.

[9] M. J. Fotheringham and M. G. Sawyer, "Adherence to recommended medical regimens in childhood and adolescence," *Journal of Paediatrics and Child Health*, vol. 31, no. 2, pp. 72–78, 1995.

[10] C. A. Jackevicius, M. Mamdani, and J. V. Tu, "Adherence with statin therapy in elderly patients with and without acute coronary syndromes," *Journal of the American Medical Association*, vol. 288, no. 4, pp. 462–467, 2002.

[11] J. A. Cramer, R. Rosenheck, G. Kirk, W. Krol, and J. Krystal, "Medication compliance feedback and monitoring in a clinical trial: predictors and outcomes," *Value in Health*, vol. 6, no. 5, pp. 566–573, 2003.

[12] R. B. Haynes, H. P. McDonald, and A. X. Garg, "Helping patients follow prescribed treatment: clinical applications," *Journal of the American Medical Association*, vol. 288, no. 22, pp. 2880–2883, 2002.

[13] D. G. Fan, "Methods for assessment and improving of compliances of clinical trial subjects," *Journal of China Prescription Drug*, vol. 97, no. 4, pp. 70–72, 2010.

[14] B. X. Zhang, L. H. Zhang, L. H. Wang, D. M. Chen, Q. Qian, and X. Y. Feng, "Effect of telephone follow-up on medication compliance after discharge in acute cerebral infarction patients," *Nursing Practice and Research*, vol. 8, no. 10, pp. 133–134, 2013.

[15] M. F. Shi, "SMS education for adherence of young and middle-aged patients with diabetes treatment," *Nei Mongol Journal of Traditional Chinese Medicine*, vol. 29, no. 2, p. 108, 2013.

[16] L. H. Tan, M. F. Huang, and T. H. You, "A survey about family support on diet treatment compliance of patients with diabetic," *Journal of Qiqihar University of Medicine*, vol. 34, no. 7, pp. 955–957, 2013.

[17] S. Zhang, H. M. Ma, L. Y. Wu, and X. Xu, "Effect of community health education for treatment compliance of patients with type 2 diabetes in China: a Meta-analysis," *China Medical Herald*, vol. 10, no. 19, pp. 20–25, 2013.

[18] S. A. Shumaker, E. Dugan, and D. J. Bowen, "Enhancing adherence in randomized controlled clinical trials," *Controlled Clinical Trials*, vol. 21, no. 5, pp. 226S–232S, 2010.

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Review Article

The Effects of Wenxin Keli on P-Wave Dispersion and Maintenance of Sinus Rhythm in Patients with Paroxysmal Atrial Fibrillation: A Meta-Analysis of Randomized Controlled Trials

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Objective. To evaluate the beneficial and adverse effects of Wenxin Keli (WXKL), alone or combined with Western medicine, on P-wave dispersion (Pd) and maintenance of sinus rhythm for the treatment of paroxysmal atrial fibrillation (PAF). *Methods*. Seven major electronic databases were searched to retrieve randomized controlled trials (RCTs) designed to evaluate the clinical effectiveness of WXKL, alone or combined with Western medicine, for PAF, with Pd or maintenance rate of sinus rhythm as the main outcome measure. The methodological quality of the included studies was assessed using criteria from the Cochrane Handbook for Systematic Review of Interventions, version 5.1.0, and analysed using RevMan 5.1.0 software. *Results*. Fourteen RCTs of WXKL were included. The methodological quality of the trials was generally evaluated as low. The results of meta-analysis showed that WXKL, alone or combined with Western medicine, was more effective in Pd and the maintenance of sinus rhythm, compared with no medicine or Western medicine alone, in patients with PAF or PAF complicated by other diseases. Seven of the trials reported adverse events, indicating that the safety of WXKL is still uncertain. *Conclusions*. WXKL, alone or combined with Western medicine, appears to be more effective in improving Pd as well as maintenance of sinus rhythm in patients with PAF and its complications.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia contributing to an epidemic of cardiovascular disease that has emerged in the new millennium. It is responsible for considerable morbidity and mortality. The advent of catheter ablation for patients with AF has provided new insights into the relative contribution of AF to left ventricular dysfunction [1]. Paroxysmal atrial fibrillation (PAF) has the tendency to develop into persistent atrial fibrillation and permanent atrial fibrillation, so the longer the duration of AF, the greater the difficulty of the treatment [2]. AF and heart failure (HF) often coexist [3]. AF patients with HF, particularly patients with HF and reduced ejection fraction, experience heavy symptom and hospitalization burdens and have relatively low rates of AF control. So, more studies are needed to identify ways to improve the management and treatment outcomes of this very high-risk patient population.

P-wave dispersion (Pd) and P maximum (Pmax) are new concepts proposed by Dilaveris et al. in 1998 that are simple electrocardiographic markers that can be used for the prediction of idiopathic PAF. The increase of Pd and Pmax is an important indicator of subsequent attacks of PAF and the tendency towards persistent atrial fibrillation [4]. Observational study had investigated the predictive power of P-wave dispersion (PWD) for the incidence of postcardiac surgery AF [5]. It determined that minimum P-wave duration, PWD, and low ejection fraction can be used for patient risk stratification of AF after coronary artery bypass grafting surgery. These years P maximum/P dispersion and high-sensitivity C-reactive protein (hs-C-reactive protein) also have been proposed as useful markers for predicting the history and recurrence of AF [6]. It indicated that subclinical inflammation may be associated with delayed/inhomogeneous atrial activation in hypertensive patients affected by AF.

Despite the fact that the use of radiofrequency and cryoablation has made significant progress, antiarrhythmic drug therapy for AF is still the preferred option for controlling heart rate [7]. The curative effect of pure Western medicine on PAF is still unsatisfactory. During long-term Western medicine treatment, typical side effects accrue [8]. Therefore, it is particularly necessary to explore traditional Chinese medicine for the treatment of PAF and to give full consideration to the role of Chinese medicine in PAF treatment. The clinical achievements of the past 30 years have indicated that integrative medicine, which builds on the combination of both Western medicine and traditional Chinese medicine, has made tremendous contributions for the great rejuvenation of the Chinese nation and human health care [9].

Wenxin Keli (WXKL) is a pure Chinese medicine, developed by Guang'anmen Hospital, Chinese Academy of Chinese Medical Sciences, that has a moderate antiarrhythmic effect. Studies have shown that it can significantly improve patient heart palpitations, chest tightness, shortness of breath, fatigue, insomnia, and other symptoms and that it can have a significant effect on controlling a variety of arrhythmias, right ventricular contractions, atrial premature contractions, AF, and sinus tachycardia. It is safe, reliable, has no side effects, and is appropriate for long-term use [10]. WXKL is reported to be effective in the treatment of atrial and ventricular cardiac arrhythmias. Data provided support for the hypothesis that WXKL, particularly in combination with quinidine, effectively suppresses arrhythmogenesis in an experimental model of Brugada syndrome via inhibition of Ito and indirect adrenergic sympathomimetic effects [11]. The latest study indicated that Wenxin Keli could suppress atrial substrate remodelling after epicardial ganglionic plexi ablation [12].

Currently, WXKL combined with antiarrhythmic drugs, a new integrative medicine therapy, has been widely used as an alternative and effective method for AF in China. A large number of clinical studies reported the clinical effect of WXKL and WXKL combined with antiarrhythmic drugs. And, until now, a large number of randomized controlled trials (RCTs) and case series have been published but have not been evaluated according to the PRISMA systematic review standard. And the predictive value of Pd on PAF in patients treated with WXKL has not been determined. Understanding the effect of WXKL on Pd and maintenance rate of sinus rhythm could be valuable for the management of PAF. Therefore, this study aims to assess the current clinical evidence of WXKL combined with antiarrhythmic drugs for PAF and seeks to identify the relationship between Pd and PAF in patients treated with WXKL and evaluate the efficacy and safety of WXKL for the treatment of PAF.

2. Materials and Methods

2.1. Database and Search Strategies. The literature search was conducted using the Chinese National Knowledge Infrastructure (CNKI), the Chinese Biomedical Literature Database (CBMdisc), the Chinese Scientific Journal Database (VIP), Wanfang Database, EMbase, PubMed, and the Cochrane Library. The search concluded in May, 2013. Other relative research papers were searched by hand. The following search terms were used individually or in combination: "Wenxin Keli," "Wenxinkeli," "Wenxin Granules," "Wenxin Granule," "atrial fibrillation," "auricular fibrillation," and "randomized controlled trial." The bibliographies of the included studies were searched for additional references.

2.2. Inclusion and Exclusion Criteria. All RCTs of patients with PAF that studied prescriptions based on WXKL, alone or combined with Western medicine, compared with no medicine or Western medicine alone were included. There were no restrictions on language, population characteristics, and publication type. The primary outcome measure was Pd or maintenance of sinus rhythm, and the secondary outcome measure was adverse drug reaction (ADR). Duplicated publications reporting the same groups of participants were excluded.

2.3. Data Extraction and Quality Assessment. Two authors independently conducted the literature search, literature screening, and data extraction. The extracted data included the title of the study, authors, year of publication, article source, study size, total number of cases, grouping, diagnosis standard, details of methodological information, and treatment process as well as the details of the control interventions, outcomes, and adverse effects for each study. Disagreement was resolved by discussion, and consensus was reached through a third party. The methodological quality of included trials was assessed according to the Cochrane Handbook for Systematic Review of Interventions, Version 5.1.0 [13], to address the following seven criteria: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias. The quality of all included trials was categorised as low, unclear, or high risk of bias ("Yes" indicates a low risk of bias, "No" indicates a high risk of bias, and "Unclear" is otherwise). Then the included trials were sorted into three categories: low risk of bias (all of the criteria were rated as having low risk of bias), unclear risk

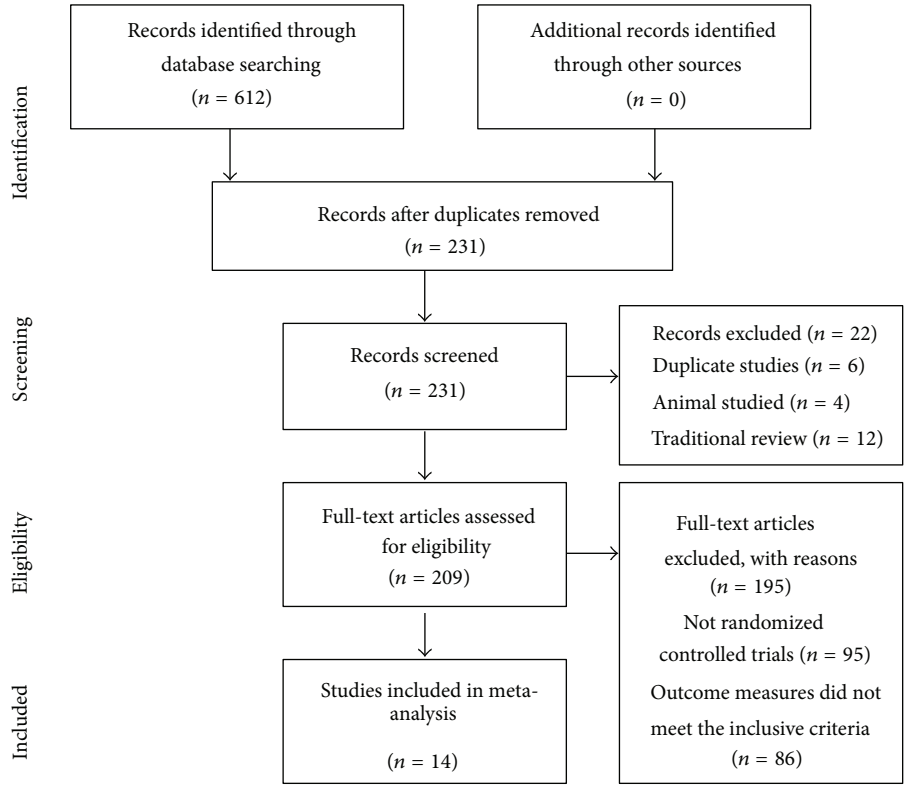

Figure 1: Flow chart of articles selection process.

of bias (at least one item was unclear), or high risk of bias (at least one item was at a high risk of bias).

2.4. Data Synthesis. RevMan 5.1.0 software provided by the Cochrane Collaboration was used for data analyses. Dichotomous data were expressed as relative risk (RR) and continuous outcomes were presented as weighted mean difference (WMD), while 95% confidence intervals (CI) were calculated for both. Meta-analysis was performed if the intervention, control, and outcomes were the same or similar. The statistical heterogeneity was presented as significant when the I square (I^2) value exceeded 50% or $P < 0.1$. In the absence of significant heterogeneity, we pooled data using fixed effects model ($I^2 < 50\%$); otherwise we used random effects model ($I^2 > 50\%$) [13]. Publication bias would be explored using funnel plot analysis if a sufficient number of studies were found.

3. Results

3.1. Description of the Included Trials. After the primary search of the seven databases both in Chinese and English, 612 articles were retrieved: Cochrane Library ($n = 3$), PubMed ($n = 5$), Embase ($n = 7$), CNKI ($n = 177$), VIP ($n = 142$), CBMdisc ($n = 193$), and Wanfang ($n = 85$). The majority were excluded because some papers were found in more than one database and some included irrelevant titles and abstracts. Only 231 studies were retrieved. Following reviews of the titles and abstracts, several studies were excluded, and only 209 studies remained. Six trials were excluded because of duplicated publication, four trials were excluded for being animal studies, and the twelve trials were excluded for being nonclinical trials, including case reports and traditional reviews. In the end, 195 out of the remaining 209 articles were excluded based on the inclusion criteria, which left fourteen RCTs to be reviewed [14–27]. The screening process is summarised in a flow chart (Figure 1). All of the trials were conducted in China and published in Chinese. The characteristics of the fourteen RCTs are summarised in Table 1.

The fourteen RCTs involved a total number of 1180 patients with PAF. Only three trials [18, 21, 27] specified diagnostic criteria of PAF. Of those three trials, two [18, 21] used an international consensus on nomenclature and classification of AF developed by the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (ESC-NASPE 2003) and Chinese Guidelines for the Management of Hypertension-2005 (CGMH-2005). The third [27] used ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation (ACC/AHA/ESC 2006). The rest of the trials [14–17, 19, 20, 22–26] only demonstrated patients with PAF diagnosis by electrocardiogram and 24-hour Holter without detailed information, and one of the trials [16] used Guidelines for the Management of Hypertension-2005 (CGMH-2005) as the diagnostic criteria for hypertension.

The interventions of all fourteen trials [14–27] included WXKL, alone or combined with Western medicine, as shown

Table 1: Characteristics and methodological quality of the included studies.

Study	Sample size (treatment/ control)	Diagnosis standard	Complications	Intervention	Control	Treatment course (month)	Clinical standards	Outcome measure
Cheng 2007 [14]	99 (53/46)	Diagnostic criteria for PAF (unclear)	PAF	WXKL 9 g tid + control	Enteric-coated aspirin	3	Clinical guideline of new drugs for TCM (1995)	Pd
Jin 2011 [15]	60 (30/30)	Diagnostic criteria for PAF (unclear)	PAF	WXKL 9 g tid	Conventional therapy (no detailed information)	6	Unclear	Pd
Zhang et al. 2008 [16]	141 (72/69)	Diagnostic criteria for PAF (unclear) CGMH (2005)	Elderly hypertension and PAF	WXKL 9 g qd	Amiodarone	2	24 h Holter	Pd, ADR
Lv et al. 2010 [17]	120 (60/60)	Diagnostic criteria for PAF (unclear)	Elderly PAF	WXKL 9 g tid + control	Amiodarone	12	Clinical guideline of new drugs for TCM (1995)	Pd, ADR
Dong et al. 2010 [18]	86 (42/40)	ESC-NASPE (2003) CGMH (2005)	Hypertension and PAF	WXKL 9 g tid + fluvastatin	Conventional therapy (no detailed information)	12	Unclear	Pd, ADR
Yan et al. 2011 [19]	80 (40/40)	Diagnostic criteria for PAF (unclear)	PAF	WXKL 5 g qd + control	Amiodarone	12	Unclear	Pd, maintenance rate of sinus rhythm
Zhang 2012 [20]	76 (38/38)	Diagnostic criteria for PAF (unclear)	PAF	WXKL 5 g tid + control	Amiodarone	6	National integrative arrhythmia prevention research symposium revised standard	Pd
Lu et al. 2010 [21]	68 (34/34)	ESC-NASPE (2003) CGMH (2005)	Elderly hypertension and PAF	WXKL 9 g tid + fluvastatin	Conventional therapy (no detailed information)	6	Unclear	Pd, maintenance rate of sinus rhythm, ADR
Zhang et al. 2011 [22]	115 (59/56)	Diagnostic criteria for PAF (unclear)	Elderly DHF and PAF	WXKL 9 g tid	Conventional therapy (no detailed information)	3	Antiarrhythmic drug therapy recommenda-tions (2001)	Pd
Xie and Shen 2006 [23]	26 (12/14)	Diagnostic criteria for PAF (unclear)	PAF	WXKL 9 g tid + irbesartan	Amiodarone	6	Unclear	Maintenance rate of sinus rhythm, ADR
Xu 2008 [24]	87 (44/43)	Diagnostic criteria for PAF (unclear)	PAF	WXKL 9 g tid + valsartan	Amiodarone	24	Unclear	Maintenance rate of sinus rhythm
Gao 2012 [25]	60 (30/30)	Diagnostic criteria for PAF (unclear)	Hypertension and PAF	WXKL 9 g tid + control	Valsartan	12	Unclear	Maintenance rate of sinus rhythm
Li et al. 2008 [26]	62 (32/30)	Diagnostic criteria for PAF (unclear)	PAF	WXKL 9 g tid + control	Amiodarone	6	Unclear	Maintenance rate of sinus rhythm, ADR
Zheng and Zhang 2013 [27]	100 (50/50)	ACC/AHA/ESC (2006)	PAF	WXKL 9 g tid + control	Amiodarone	9	Unclear	Maintenance rate of sinus rhythm, ADR

Table 2: Quality assessment of the included randomized controlled trials.

Included trials	Sequence generation	Allocation concealment	Blinding of participants personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Risk of bias
Cheng 2007 [14]	Unclear	Unclear	Unclear	Unclear	Unclear	No	Unclear	High
Jin 2011 [15]	Unclear	Unclear	Unclear	Unclear	Unclear	No	Unclear	High
Zhang et al. 2008 [16]	Unclear	Unclear	Unclear	Unclear	Unclear	No	Unclear	High
Lv et al. 2010 [17]	Unclear	Unclear	Double-blind method	Unclear	Yes	No	Unclear	Unclear
Dong et al. 2010 [18]	Unclear	Unclear	Unclear	Unclear	Yes	No	Unclear	High
Yan et al. 2011 [19]	Unclear	Unclear	Unclear	Unclear	No	No	Unclear	High
Zhang 2012 [20]	Unclear	Unclear	Unclear	Unclear	Unclear	No	Unclear	High
Lu et al. 2010 [21]	Unclear	Unclear	Unclear	Unclear	Yes	No	Unclear	High
Zhang et al. 2011 [22]	Odd and even numbers	Unclear	Double-blind method	Unclear	Unclear	No	Unclear	Unclear
Xie and Shen 2006 [23]	Table of random number	Unclear	Unclear	Unclear	Unclear	No	Unclear	Unclear
Xu 2008 [24]	Unclear	Unclear	Unclear	Unclear	Unclear	No	Unclear	High
Gao 2012 [25]	Unclear	Unclear	Unclear	Unclear	Unclear	No	Unclear	High
Li et al. 2008 [26]	Unclear	Unclear	Unclear	Unclear	Yes	No	Unclear	High
Zheng and Zhang 2013 [27]	Unclear	Unclear	Unclear	Unclear	Yes	No	Unclear	High

in Table 1. The controls included Western medicine alone or no medicine use. The total treatment duration ranged from two months to 24 months. Only four trials [14, 17, 20, 22] specified clinical standards of PAF. Nine of the fourteen trials [14–22] used the Pd as the main outcome measure, and seven of the fourteen trials [19, 21, 23–27] used the maintenance of sinus rhythm as the main outcome measure. Half of the included trials [16–18, 21, 23, 26, 27] described adverse effects in detail.

3.2. Methodological Quality of the Included Trials. The majority of the included RCTs were assessed to be of low methodological quality. According to the predefined quality assessment criteria indicated above, none of the included trials were evaluated as having a low risk of bias as shown in Table 2. Only two [22, 23] of the fourteen trials reported the methodology used to generate the allocation sequence. One [22] stated the method as odd and even numbers, and the other [23] used the table of random numbers method but without any detailed information; therefore, insufficient information was provided to allow quality assessment of the allocation method. Allocation concealment was not mentioned in every included trial. Two trials [17, 22] used the double-blind method to blind participants and personnel, but blinding of outcome assessment was not detailed in all of the trials. Only five trials [17, 18, 21, 26, 27] reported dropout or withdrawal and ten trials [14, 15, 17–19, 21, 23, 24, 26, 27] mentioned follow-up. None of the trials calculated an estimation of the pre-trial sample size, which indicated a lack of statistical power to ensure appropriate estimation of the therapeutic effect. Selective reporting was generally unclear in the trials due to the inaccessibility of the protocol. The results of the assessment of risk of bias are presented in Table 2.

3.3. Effects of the Interventions

3.3.1. P-Wave Dispersion. Nine trials [14–22] used the reduction of Pd as an outcome measure. No significant difference in Pd before treatment was observed between the WXKL, alone or combined with Western medicine, group (experimental group) and Western medicine group (control group). This allowed for a comparison of Pd value of the two groups after treatment. Trial results for the nine independent trials were not homogeneous, $\text{Chi}^2 = 129.71$, df = 8, ($P < 0.00001$); $I^2 = 94\%$, requiring the use of the random effects model for statistical analysis. The Pd after WXKL, alone or combined with Western medicine, treatment was lower than Western medicine treatment. The meta-analysis demonstrated a significant difference between the two groups for each of the three criteria outcome measures (MD: −7.65 [−11.73, −3.56]; $P = 0.0002$) (Figure 2).

3.3.2. Maintenance Rate of Sinus Rhythm. Seven trials [19, 21, 23–27] used the maintenance rate of sinus rhythm at six months following treatment as an outcome measure. These seven trials compared the combination of WXKL plus Western medicine with Western medicine alone. Trial results for the seven independent trials were homogeneous, $\text{Chi}^2 = 4.79$, df = 6, ($P = 0.57$); $I^2 = 0\%$, requiring the use

Study or subgroup	Experimental			Control				Mean difference	Mean difference
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Cheng 2007 [14]	16.31	6.54	53	34.98	6.55	46	11.4%	−18.67 [−21.26, −16.08]	
Dong et al. 2010 [18]	46	8	42	50	7	40	11.2%	−4.00 [−7.25, −0.75]	
Jin 2011 [15]	36.58	2.79	24	43.43	5.04	30	11.6%	−6.85 [−8.97, −4.73]	
Lu et al. 2010 [21]	48	8	32	53	9	31	10.6%	−5.00 [−9.21, −0.79]	
Lv et al. 2010 [17]	40.28	7.32	60	45.21	6.74	58	11.5%	−4.93 [−7.47, −2.39]	
Yan et al. 2011 [19]	37.6	8.6	40	42.5	12.2	40	10.4%	−4.90 [−9.53, −0.27]	
Zhang 2012 [20]	46.05	8.25	38	50.64	7.82	38	11.0%	−4.59 [−8.20, −0.98]	
Zhang et al. 2008 [16]	40	9	72	42	7	69	11.4%	−2.00 [−4.66, 0.66]	
Zhang et al. 2011 [22]	28.86	10.77	59	46.57	9.95	56	10.9%	−17.71 [−21.50, −13.92]	
Total (95% CI)			**420**			**408**	**10.0%**	**−7.65 [−11.73, −3.56]**	

Heterogeneity: $\tau^2 = 36.25$; $\chi^2 = 129.71$, df = 8 ($P < 0.00001$); $I^2 = 94\%$

Test for overall effect: $Z = 3.67$ ($P = 0.0002$)

−100 −50 0 50 100

Favours experimental Favours control

Figure 2: Analysis of P-wave dispersion. Forest plot of comparison: WXKL combined with Western medicine treatment group versus Western medicine treatment group.

Study or subgroup	Experimental		Control			Risk ratio	Risk ratio
	Events	Total	Events	Total	Weight	M-H, fixed, 95% CI	M-H, fixed, 95% CI
Gao 2012 [25]	22	30	13	30	8.7%	1.69 [1.07, 2.69]	
Li et al. 2008 [26]	26	32	17	30	11.8%	1.43 [1.01, 2.04]	
Lu et al. 2010 [21]	28	32	19	31	12.9%	1.43 [1.05, 1.94]	
Xie and Shen 2006 [23]	11	12	8	14	4.9%	1.60 [0.99, 2.60]	
Xu 2008 [24]	39	44	29	43	19.7%	1.31 [1.04, 1.66]	
Yan et al. 2011 [19]	33	40	30	40	20.1%	1.10 [0.87, 1.38]	
Zheng and Zhang 2013 [27]	44	50	32	48	21.9%	1.32 [1.05, 1.65]	
Total (95% CI)		**240**		**236**	**100.0%**	**1.35 [1.21, 1.51]**	
Total events	203		148				

Heterogeneity: $\chi^2 = 4.79$, df = 6 ($P = 0.57$); $I^2 = 0\%$

Test for overall effect: $Z = 5.26$ ($P < 0.00001$)

0.01 0.1 1 10 100

Favours experimental Favours control

Figure 3: Analysis of maintaining sinus rhythm rate after six months of treatment. Forest plot of comparison: WXKL combined with Western medicine treatment group versus Western medicine treatment group.

of the fixed effects model for statistical analysis. The rate of maintenance of sinus rhythm in the WXKL combined with Western medicine group (experimental group) was greater than that of the Western medicine group (control group). The rates of maintenance of sinus rhythm in the two groups were 84.6% and 62.7%, respectively. The meta-analysis showed that there was a significant beneficial effect in the combination group compared with the Western medicine alone group (RR 1.35; 95% CI [1.21, 1.51]; and $P < 0.00001$) (Figure 3).

3.4. Sensitivity Analysis, Subgroup Analysis, and Publication Bias. To examine the stability of the results, the fixed effects model was used to perform meta-analysis of Pd instead of the random effects model. The random effects model was used instead of the fixed effects model to analyse the maintenance of sinus rhythm. A significant difference was observed in the Pd of the two groups for the three criteria outcome measures (MD: −7.74 [−8.73, −6.75]; $P < 0.00001$). There was also a significant difference between the WXKL combined with Western medicine group and the Western medicine alone group in the maintenance of sinus rhythm (RR 1.32; 95%CI [1.18, 1.47]; and $P < 0.00001$). Given that the results of the two methods were consistent, stability was considered to be sufficient. The number of trials was too small to conduct analysis of subgroup analysis and also failed to perform funnel plot to detect publication bias.

3.5. Adverse Effects. Seven out of the included trials [16–18, 21, 23, 26, 27] described adverse effects in detail. One trial [16] mentioned adverse effects in both groups with one case of dry mouth and nausea, and two cases of sinus bradycardia in the WXKL group, two cases of dizziness and nausea, two cases of sinus bradycardia, one case of II atrioventricular block, and one case of Q-T interval prolongation in the amiodarone group. Three trials [17, 26, 27] mentioned specific symptoms, including vomiting, nausea, sinus bradycardia, Q-T interval prolongation, hyperthyroidism, stomach discomfort, and cough in the WXKL combined with amiodarone group and vomiting, nausea, sinus bradycardia, and hyperthyroidism in the amiodarone group. These side effects may be related to the adverse effect of amiodarone. One trial [23] reported adverse effects in the WXKL combined with irbesartan group including sinus bradycardia, mildly abnormal thyroid function, stomach discomfort, and fatigue. None of the adverse events

were serious. Two trials [18, 21] reported adverse effects in the WXKL combined with fluvastatin group, including mildly abnormal liver function, which may be an adverse effect of fluvastatin. In total, the incidence of adverse reactions was lower in the treatment group compared with the control group.

4. Discussion

This systematic review included fourteen RCTs with a total of 1180 participants. The main findings of this systematic review were that WXKL combined with Western medicine demonstrated the potential effect of lowering Pd and improving the maintenance of sinus rhythm when compared with Western medicine alone or no treatment. WXKL is an effective treatment for patients with PAF. However, due to the poor methodological quality of the included studies, the evidence remains weak. Thus, the available data are not adequate to draw a definite conclusion of the efficacy of WXKL for PAF, but they provide some encouraging evidence of the effect of WXKL for the treatment of PAF. Nine trials used the reduction of Pd as an outcome measure and trial results for the nine independent trials were not homogeneous. The main source of the heterogeneity may have several aspects. The treatment courses are not the same, the longest is 24 month, while the shortest is 2 month. The dosage and the time of WXKL the patients used were also consistent. Because of different diagnosis standards, different doctors' diagnosis can make a big difference. So the clinical and methodological source made the heterogeneity of statistics.

AF is one of the most common chronic arrhythmia conditions associated with an adverse prognosis. Many studies show that subjects with AF have markedly reduced survival compared with subjects without AF and that AF is independently associated with a 50% to 90% increase in the risk of death. Therefore, the effective treatment and prevention of AF has important clinical significance [28]. Many studies have shown that atrial electrical remodelling and structural remodelling of AF are the main mechanism for precipitating and maintaining sinus rhythm. Electrical remodelling could shorten atrial refractoriness and contributes to an increase in the stability of AF. Atrial structural remodelling occurs as a result of heart failure and other underlying cardiovascular diseases [29, 30]. The ionic mechanisms underlying this arrhythmogenic process have been elucidated by a number of patch clamp experiments in isolated atrial cells from animal models and patients in chronic AF. The most important impact of AF on the ion channels was a marked reduction in the L-type Ca^{2+} current [31].

AF is a commonly encountered arrhythmia that occurs in patients after coronary artery bypass surgery (CABG). A study has shown that the preoperative signal averaged ECG (SAECG) Pd was the best predictor of AF after CABG [32]. Pd is an appealing marker for predicting the risk of developing atrial fibrillation. The increase of Pd is a good predictor of the occurrence of PAF and it is also an important electrophysiological cause of AF [33]. However, a study showed that this technique has limited sensitivity and specificity because there is overlap between the wide range of values of Pd, Pmax, and Pmin in healthy individuals that overlaps with those of patients with increased risk for AF. This may stem from methodological issues; therefore, there is a definite need for methodological standardisation of Pd measurements [34]. Most pharmacologic therapies and electrical cardioversion for AF unsuccessfully treat the atrial electrical remodelling and structural remodelling of AF [35], so it is particularly necessary to explore traditional Chinese medicine for the treatment of PAF.

WXKL is the first antiarrhythmic Chinese medicine to be approved by the state. It is developed from the application of traditional medicine theory combined with the essence of Chinese and Western medicine theory. It composed of five main components: nardostachys chinensis batal extract, codonopsis, notoginseng, amber, and rhizoma polygonati. A study has shown that WXKL is a novel atrial elective sodium channel blocker and is effective in suppressing AF and preventing its induction [36]. From the included articles, we can see WXKL has significant effect on improving the main symptoms such as headache, dizziness, palpitations, and insomnia. This meta-analysis showed that WXKL combined with Western medicine demonstrated the potential effect of lowering Pd and improving the maintenance of sinus rhythm.

However, this systematic review has the following limitations. Firstly, the quality of the methodology of the RCTs included in this systematic review is generally low. All of the included trials claimed randomisation, but only two of them [22, 23] reported the methodology used to generate the allocation sequence. The other trials mentioned only that "patients were randomized into two groups," indicating potential selection bias. Two trials [17, 22] mentioned the double-blind method of blinding participants and personnel but did not provide sufficient information for quality assessment, which might lead to potential performance bias and detection bias. Five of the trials [14, 15, 20, 24, 25] were conducted by a single author, which could lead to performance bias. Only five trials [17, 18, 21, 26, 27] reported dropout or withdrawal, but without the intention-to-treat analysis. And ten RCTs [14, 15, 17–19, 21, 23, 24, 26, 27] mentioned follow-up. None of trials gave a pretrial estimation of sample size, which could indicate a lack of statistical power to ensure appropriate estimation of the therapeutic effect. It is well known that the trials that are poorly designed methodologically show larger differences compared with rigorously conducted trials. Additionally, all of the trials were conducted in China and published in Chinese, leading to publication bias. All of the RCTs claimed that the positive effect of WXKL combined with Western medicine is better than Western medicine alone or no medicine. While no negative findings have been reported, we cannot eliminate the possibility of the unpublished material.

Secondly, the safety of Chinese herbal medicines is of general concern. Adverse effects were reported in seven out of the fourteen included trials [16–18, 21, 23, 26, 27]. Some adverse effects were not severe and patients spontaneously recovered without special treatment. However, some adverse effects are irreversible. In total, the incidence of adverse reactions was lower in experimental groups compared with the control

groups. The other seven trials did not report any adverse effects. Due to the limited evidence provided by the eligible trials, conclusions about the safety of WXKL combined with Western medicine cannot be drawn from this study. In the future, larger-scale clinical trials with long-term follow-up are warranted to properly assess the safety of WXKL therapy.

Thirdly, publication and other biases may play an important role. We only identified and included trials published in Chinese and most of the trials are small sample with positive findings. We tried to avoid language bias and location bias, but we cannot exclude potential publication bias. During the articles assessed for eligibility, we found that the majority was excluded because of no detailed information and the quality of the methodology of the RCTs included in this systematic review is generally low. We recommend that future researchers should follow the basic guidelines for reporting clinical trials conducted with clear TCM diagnostic criteria.

In addition, the currently available antiarrhythmic drugs for PAF suffer from limited safety and efficacy, probably because they were not designed based on specific pathological mechanisms. We should clarify the main pathological mechanisms of AF, understand traditional and novel aspects of antiarrhythmic drugs in relation to these pathological mechanisms, and present potential therapeutic approaches, including restoring abnormal Ca^{2+} handling in AF, structure-based modulation of atrial-specific cardiac ion channels, and targeting atrial remodelling. Moreover, we should continue to expand the cumulative meta-analysis of future trials, especially RCTs, and choose possible predictors of PAF to provide more meaningful clinical indicators for clinicians.

In summary, there is an encouraging evidence of the effect of WXKL, alone or combined with Western medicine, on Pd and the maintenance of sinus rhythm in patients with PAF. After treatment with WXKL, there is a significant reduction in Pd in patients with PAF, and the maintenance of sinus rhythm is significantly improved. Due to the poor quality of experimental design and methodology, the evidence remains weak. More rigorous RCTs with strong design and high methodological quality will be needed to present a high level of evidence for the effectiveness of WXKL in treating PAF.

Conflict of Interests

All authors declare that they have no conflict of interests.

Authors' Contribution

Yu Chen, Shaoping Nie, Hai Gao, and Tao Sun contributed equally to this paper.

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References

[1] R. Balasubramaniam and P. M. Kistler, "Atrial fibrillation in heart failure: the chicken or the egg?" *Heart*, vol. 95, no. 7, pp. 535–539, 2009.

[2] D.-Y. Hu and J.-G. Yang, "Core treatment strategy for atrial fibrillation in China," *Chinese journal of internal medicine*, vol. 47, no. 2, pp. 93–95, 2008.

[3] J. Silva-Cardoso, O. J. Zharinov, P. Ponikowski et al., "Heart failure in patients with atrial fibrillation is associated with a high symptom and hospitalization burden: the realiseAF survey," *Clinical Cardiology*, 2013.

[4] P. E. Dilaveris, E. J. Gialafos, S. K. Sideris et al., "Simple electrocardiographic markers for the prediction of paroxysmal idiopathic atrial fibrillation," *American Heart Journal*, vol. 135, no. 5 I, pp. 733–738, 1998.

[5] J. M. Hashemi, A. Amirpour, R. Zavvar et al., "Predictive value of P-wave duration and dispersion in post coronary artery bypass surgery atrial fibrillation," *ARYA Atherosclerosis*, vol. 8, no. 2, pp. 59–62, 2012.

[6] A. Mazza, M. G. Bendini, M. Cristofori et al., "C-reactive protein and P-wave in hypertensive patients after conversion of atrial fibrillation," *Journal of Cardiovascular Medicine*, vol. 14, no. 7, pp. 520–527, 2012.

[7] V. Fuster, L. E. Rydén, D. S. Cannom et al., "2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society," *Journal of the American College of Cardiology*, vol. 57, no. 11, pp. e101–e198, 2011.

[8] C. Sohns and M. Zabel, "Current role of amiodarone in antiarrhythmic therapy," *Herzschrittmachertherapie und Elektrophysiologie*, vol. 21, no. 4, pp. 239–243, 2010.

[9] J. Wang and X. J. Xiong, "Current situation and perspectives of clinical study in integrative medicine in China," *Evidence-Based Complementary and Alternaivet Medicine*, vol. 2012, Article ID 268542, 11 pages, 2012.

[10] X. C. Liu and Z. Y. Liu, "The efficacy of Buchang wenxin particle for the treatment of paroxysmal atrial fibrillation," *Practical Clinical Journal of Integrated Traditional Chinese and Western Medicine*, vol. 4, no. 2, pp. 50–51, 2004.

[11] Y. Minoura, B. K. Panama, V. V. Nesterenko et al., "Effect of Wenxin Keli and quinidine to suppress arrhythmogenesis in an experimental model of Brugada syndrome," *Heart Rhythm*, vol. 10, no. 7, pp. 1054–1062, 2013.

[12] J. Xiao, Q. Zhao, A. H. Kebbati et al., "Wenxin Keli suppresses atrial substrate remodelling after epicardial ganglionic plexi ablation," *Experimental & Clinical Cardiology*, vol. 18, no. 2, pp. 153–157, 2013.

[13] J. P. T. Higgins and S. Green, *Cochrane Handbook For Systematic Reviews of Interventions*, The Cochrane Collaboration, 2011.

[14] J. D. Cheng, "Clinical observation of Wenxin Keli for the treatment of paroxysmal atrial fibrillation," *Chinese Journal of Information on Traditional Chinese Medicine*, vol. 14, no. 8, pp. 55–56, 2007.

[15] S. R. Jin, "The effect of Wenxin keli on P wave dispersion and the treatment for the paroxysmal atrial fibrillation," *Chinese Journal of Modern Drug Application*, vol. 5, no. 12, pp. 92–93, 2011.

[16] Z. M. Zhang, P. Bai, and J. Z. Lin, "Wenxin Keli combined with ethylamine iodine skin ketone in treating senile hypertension paroxysmal atrial fibrillation," *Chinese Journal of Hypertension*, vol. 16, no. 12, pp. 1134–1135, 2008.

[17] N. Lv, D. Lin, and P. Lin, "Wenxin granule and low dose amiodarone in treating 60 cases of senile parokysmal atrial fibrillation," *Fujian Journal of Traditional Chinese Medicine*, vol. 41, no. 3, pp. 7–8, 2010.

[18] Y. Dong, L. F. Xing, B. M. Li, and C. J. Tong, "Effect of Wenxin particle combine with fluvastatin on atrial remodelling in essential hypertension patients with atrial fibrillation," *Chinese Journal of Difficult and Complicated Cases*, vol. 9, no. 8, pp. 566–568, 2010.

[19] Y.-J. Yan, Y.-M. Zhang, Y. Lu, S.-Y. Wang, and H.-D. Cui, "Effect of Wenxin-Keli combined with amiodarone on dispersion of P wave and C-reactive protein in patients with paroxysmal atrial fibrillation," *Chinese Journal of New Drugs*, vol. 20, no. 15, pp. 1432–1434, 2011.

[20] C. J. Zhang, "Effect of Wenxin granule treatment for paroxysmal atrial fibrillation patients," *Practical Pharmacy and Clinical Remedies*, vol. 15, no. 11, pp. 737–739, 2012.

[21] J. L. Lu, Y. Dong, and L. F. Xing, "The maintenance of sinus rhythm in patients with elderly hypertensive paroxysmal atrial fibrillation and the intervention of Wenxin Keli combined with fluvastatin," *Hebei Medical Journal*, vol. 32, no. 24, pp. 3483–3484, 2010.

[22] M. L. Zhang, S. X. Jing, and H. Y. Zhang, "The effect of Buchangwenxin particle on dispersion of P wave in elder patients with diastolic cardiac dysfunction and paroxysmal atrial fibrillation," *Chinese Journal of Primary Medicine and Pharmacy*, vol. 18, no. 20, pp. 2756–2758, 2011.

[23] P.-Y. Xie and S.-H. Shen, "Effect of combination of Chinese and Western medicines on sinus rhythm maintenance in patients with auricular fibrillation after conversion," *Chinese journal of integrated traditional and Western medicine*, vol. 26, no. 7, pp. 644–646, 2006.

[24] S. Z. Xu, "The study of prevention and curative effect of the valsartan and wenxinkeli on the paroxysmal atrial fibrillation," *Practical Clinical Journal of Integrated Traditional Chinese and Western Medicine*, vol. 8, no. 4, pp. 6–7, 2008.

[25] B. Gao, "Clinical observationof Wenxin Keli combined with valsartan on the maintenance of sinus rhythm in patients with hypertension with paroxysmal atrial fibrillation," *Chinese Community Doctors*, vol. 14, no. 7, p. 54, 2012.

[26] F. C. Li, J. J. Tong, W. Hao, and Z. Ma, "The effect of Wenxin Keli combined with amiodaronefor the treatment of paroxysmal atrial fibrillation in 32 cases," *Shanxi Journal of Traditional Chinese Medicine*, vol. 29, no. 7, pp. 839–840, 2008.

[27] Q. H. Zheng and X. B. Zhang, "The effect of Wenxin Keli combined with amiodarone on the maintenance of sinus rhythm and serum MMP-9 in patients with paroxysmal atrial fibrillation," *Guiding Journal of Traditional Chinese Medicine and Pharmacology*, vol. 19, no. 2, pp. 36–37, 2013.

[28] E. J. Benjamin, P. A. Wolf, R. B. D'Agostino, H. Silbershatz, W. B. Kannel, and D. Levy, "Impact of atrial fibrillation on the risk of death: the Framingham Heart Study," *Circulation*, vol. 98, no. 10, pp. 946–952, 1998.

[29] M. Allessie, J. Ausma, and U. Schotten, "Electrical, contractile and structural remodeling during atrial fibrillation," *Cardiovascular Research*, vol. 54, no. 2, pp. 230–246, 2002.

[30] S. Nattel, B. Burstein, and D. Dobrev, "Atrial remodeling and atrial fibrillation: mechanisms and implications," *Circulation*, vol. 1, no. 1, pp. 62–73, 2008.

[31] L. Yue, J. Feng, R. Gaspo, G.-R. Li, Z. Wang, and S. Nattel, "Ionic remodeling underlying action potential changes in a canine model of atrial fibrillation," *Circulation Research*, vol. 81, no. 4, pp. 512–525, 1997.

[32] K. Aytemir, S. Aksoyek, N. Ozer, S. Aslamaci, and A. Oto, "Atrial fibrillation after coronary artery bypass surgery: P wave signal averaged ECG, clinical and angiographic variables in risk assessment," *International Journal of Cardiology*, vol. 69, no. 1, pp. 49–56, 1999.

[33] P. E. Dilaveris and J. E. Gialafos, "P-wave dispersion: a novel predictor of paroxysmal atrial fibrillation," *Annals of Noninvasive Electrocardiology*, vol. 6, no. 2, pp. 159–165, 2001.

[34] U. Nussinovitch, "Meta-analysis of P-wave dispersion values in healthy individuals: the influence of clinical characteristics," *Annals of Noninvasive Electrocardiology*, vol. 17, no. 1, pp. 28–35, 2012.

[35] A. G. Zaman, M. T. Kearney, C. Schecter, S. G. Worthley, and J. Nolan, "Angiotensin-converting enzyme inhibitors as adjunctive therapy in patients with persistent atrial fibrillation," *American Heart Journal*, vol. 147, no. 5, pp. 823–827, 2004.

[36] A. Burashnikov, A. Petroski, D. Hu, H. Barajas-Martinez, and C. Antzelevitch, "Atrial-selective inhibition of sodium-channel current by Wenxin Keli is effective in suppressing atrial fibrillation," *Heart Rhythm*, vol. 9, no. 1, pp. 125–131, 2012.

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Research Article

Understanding Patient Values and the Manifestations in Clinical Research with Traditional Chinese Medicine—With Practical Suggestions for Trial Design and Implementation

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Objective. To define patient values, identify their manifestations in a randomized clinical trial, and investigate the possible implications for clinical research of traditional Chinese medicine. *Methods*. We categorized patient values manifestations into patient choice, preference, compliance, and patient-reported outcomes and summarized the underlying personal values through purposeful electronic searches for relevant reports. By hypothesizing a set of positive versus negative circumstances occurring in the enrollment, intervention allocation, treatment, and the follow-up stage of a trial, it is possible to discuss the potential implications of patient values manifestation on a trial with traditional Chinese medicine. *Results*. Patient values and its manifestations are ubiquitous in the process of clinical research with traditional Chinese medicine. These values may provide motivation for participation or engender the internal and external validity of the study. *Conclusions*. Trialists should attach sufficient importance to the needs and concerns of individual participant. To incorporate patient values into the design and conduct of a clinical study with traditional Chinese medicine, researchers are recommended to adopt participant-friendly design and use patient-reported outcomes, take convenience-for-patients measures, and help foster rational beliefs and behaviors of trial participants.

1. Introduction

Patient values are depicted as the unique preferences, concerns, and expectations each patient brings to a clinical encounter in the EBM sense [1]. Personal and cultural values reflect an individual's sense of right and wrong or what one ought to do, and tend to influence attitude and behavior. In the context of clinical trials where patient engagement is most intensive, values have a wider meaning and a larger role to play. In this study, the authors defined patient values as a set of personal codes of conduct by which a patient judges what is important, makes decisions, and takes actions. Deeply grounded in a person's experiences, cultural background, economic circumstance, and religious beliefs, patient values are empirical and subjective in nature, yet susceptible to suggestions from the doctor and one's relatives and friends as well as from other factors.

In the clinical research of traditional Chinese medicine (TCM), the randomized controlled trial (RCT) design is generally acknowledged as the gold standard for efficacy assessment. It uses a prospective experimental design with unique features that enable the investigator to proactively control intervention assignment and other confounders that may inflict on the validity of the results. Properly conducted randomization can help eliminate bias in treatment assignment, facilitate the masking of treatment group, and maximize statistical power in terms of introducing equal group sizes [2].

Despite the "standard patient" and the "standard treatment procedure" claimed by pro-RCT methodologists,

the individuality of trial participants and, especially for TCM clinical research, the interactive and patient-centered nature of TCM interventions are never to be undermined. While study subjects are expected to be actively involved in the whole process of the trial, one can hardly tell why eligible candidates are unwilling to enroll, or what makes enrolled subjects refuse randomization, fail to keep a schedule, or discontinue treatment, and after all how the participants' values take a role in this. These problems need to be carefully discussed and the participants' needs and concerns need to be well incorporated into trial design and implementation to avoid detrimental effects on the trial results.

2. Materials and Methods

A number of cross-sectional surveys and interview studies [3–6] have examined similar questions, but a general picture depicting the scale of the impact of patient values on clinical research in TCM has not been fully unfolded. In this report, a preliminary attempt was made to summarize patient values and its manifestations in a hypothesized set of positive versus negative circumstances in the context of the enrollment, randomization, intervention allocation, treatment duration, and follow-up phase of a RCT. Patient values and beliefs that may impact their behavior in a clinical trial were identified through purposeful rather than comprehensive electronic searches. The finding from systematic reviews was quoted in preference to that of a survey. The RCT model was chosen because the design widely acknowledged the most rigorous way of removing extraneous factors and any potential confounding variables, but in this study we will show you why the RCTs cannot avoid influences from patient values. We categorized values' manifestations into patient choices, patient preferences, compliance, and patient-reported outcomes and provided a definition for each, identified the underpinning personal values, elaborated on possible implications, and came up with advices on study design and implementation.

3. Results

3.1. Patient Choices. Having choices and making decisions are parts of the life of patients involved in a RCT. Here, we restricted the scope of the term to refer to the act of a candidate subject choosing whether or not to enroll in the study, or to readily accept the allocated medication. Personal values cannot only influence a candidate subject's decision-making as to whether to participate by giving informed consent, and go on to impact on the enrolled participant's willingness to continue after being informed of the allocated group as in an unblinded study. For instance, patients who believe that "human energy (*qi* in Chinese *pinyin*) is consumed during acupuncture" may never volunteer for a RCT with acupuncture. Even if they do get involved, it is very likely that they will drop out of the study once they are informed about being assigned to the acupuncture group. In the case of an unsuccessful recruitment where a low proportion of eligible candidates consent or remain in the study after disclosure of allocation, the progress of clinical research will be delayed and excessive costs incurred, and the study may risk early termination.

According to two systematic reviews [3, 4] on patient-reported barriers to participation in RCTs, main causes of concern that are generally value-based involve participants' belief that they should be paid, their questioning of the treatment efficacy, a distrust of hospital or medication, and the fear for the unknown. Despite repeated searches, we failed to locate reports on patient values-based reasons for refusal of participation in the TCM clinical research. However, there is indirect evidence from a survey of 2,000 potential trial candidates in a hospital in west China which identified factors associated with the Chinese patients' unwillingness to participate in clinical research [7]. Many of them relate to personal values, which are the fear of being a "guinea pig" in the trial setting, concerns with drug safety, efficacy and side effects, and the belief that a trial participant will be marginalized as "someone special." While these factors have their roots primarily in the participant's self-belief systems, influences from the outside world such as the oppositions from an "important person" (e.g., spouse, parent, close friend) and the attitudes of their clinicians have also been reported to be capable of reshaping patients' beliefs and facilitating decision-making [4].

Therefore, it is advisable to take advantage of external influences such as education programs, consultancy services and in-depth physician-patient communication to inform knowledge, increase understanding, and resolve doubts. In clinical research of TCM, especially the potential benefits and risks of all treatment options, shall be explained in ways that the participants accept and understand, rather than using obscure TCM terminology and philosophical reasoning. Potential participants should be informed of what clinical research is, what it does, and their rights and obligations, and most importantly they are cleared of all their misunderstandings of clinical research and of the TCM therapy to be applied in pretrial consultations. Furthermore, a good doctor-patient relationship also has a role to play in enhancing the rate of successful referrals for a trial.

3.2. Patient Preferences. Patient preferences denote a patient's expressed greater interest in or desire for a treatment option than any other ones. After randomization and in intervention allocation, patients' personal values manifest themselves by making choices regarding whether or not to have the assigned medication (no matter one desired it or disliked it), on the condition that patients are aware of the treatment to be administered (such as in a design where masking of patients is not used). This suggests that unblinded studies are particularly vulnerable to possible patient preferences-induced biases.

Unfortunately, the development of methodology for trials with TCM has not been sufficiently sound to provide appropriate placebo designs for many TCM therapeutic tools (acupuncture, cupping, etc.). Therefore, the use of blinding is impractical. In placebo-controlled trials with herbal medicine or Chinese patent drug, similarly, the placebo may not be perfectly indistinguishable from real drug because the taste, color, and smell of a herbal decoction are absolutely unique.

A proportion of participants may know of the allocation during the trial, especially when they have previously taken the drug of interest. As a result, a major portion of clinical studies in TCM were unblinded. In proof of this statement, we launched a search on the Cochrane Central Register for Controlled Trials (Issue 8, 2013) to identify the number of controlled clinical trials with TCM and the ratio of blinded versus unblinded studies. It was found that only 129 among the total of 628 controlled trials used blinding. In these unblinded trials where the participants are aware of the treatment, preferences for one treatment option may influence their willingness to continue treatment, their expectations, if any, and the degree of engagement in the study. For example, patients preferring one kind of Chinese herbal medicine to the other in a trial might respond negatively to being randomized to the unopted arm.

This could lead to two possible circumstances. The first one is increased drop-outs and reduced statistical power. Findings from one systematic review [8] showed that patient preferences for a treatment option could prevent them from attending the trial or accepting the treatment assigned. If patients with strong preferences for one treatment regimen are not assigned to their opted arm, and thereby decide that they will not proceed further in the study, the implications for the trial would be much more serious than when the same withdrawals occur before randomization because this may lead to reduced comparability between groups right at the start [9]. The absence of these participants (eligible but withdraw for preferences) may restrict generalization of the results and weaken the external validity of the study [8, 10].

Secondly, if patients with strong preferences remain in the trial after being randomized to the nonopted intervention, they may fail to adhere to or passively receive the assigned treatment or even seek the other treatment option on their own [11, 12]. This leads to implications for compliance, and the contamination of interventions. On the other hand, those allocated to their preferred treatment may expect higher of the therapy, engage more actively, and believe firmer in the treatment efficacy, which all might contribute to better clinical outcomes by exerting positive psychological effects similar to the placebo effects [13]. The phenomenon has been evidenced by the findings of a systematic review and patient level meta-analysis of 17 musculoskeletal trials, which found patients randomized to their preferred treatment did better than participants who were indifferent to allocation or those who received unopted treatment [14]. However, other studies [8, 15] came to contradictory results and found insufficient empirical evidence in proof of consistent effect of preference on outcomes.

To incorporate patient preference into the design of clinical trials, preference controlled designs such as the comprehensive cohort design, the Rücker design, and the Wennberg et al. design have been proposed as alternatives to the conventional RCTs. In the comprehensive cohort setting, participants with preferences are allowed their desired treatment and those with no preferences are randomized as usual [16]. The Rücker's design randomizes half of the study sample to a choice group and the other half to a randomized group. Only participants in the choice group have the chance to choose their desired treatment or to be randomized [17]. In the Wennberg et al. design, participants are randomized to a preference group, in which all patients decide for themselves the treatment to receive, or to a randomized group.

Back to clinical trials with TCM, apart from the above mentioned difficulties in blinding, for which the patients are either aware of treatment allocation or it is easy for them to detect the allocation, the efficacy evaluation system of TCM also relies heavily on self-reported outcome measures (i.e., changes in TCM symptom scores), which are considered sensitive to personal preferences. These features are in alarming resemblance to the conditions, what Halpern [18] described as the seedbed for preference-induced biases. Furthermore, trials with nonpharmacological interventions such as acupuncture, moxibustion, and cupping involve lots of participant engagement, corresponding to what Brewin and Bradley [19] termed as the "participative interventions," in which preference effects are likely to be most apparent. In view of this, the preference controlled design provides an attractive alternative for clinical research of TCM despite the fact that it may require a larger sample, take longer, and cost more.

3.3. Patient Compliance. Compliance is narrowly defined in this paper as the extent to which a study subject follows the treatment regimen as required, in terms of taking medications, following diets, executing lifestyle changes, or paying visits [5], during treatment and followup. In trials with TCM treatment regimens where patient motivation and engagement play a key role, compliance or noncompliance behaviors on the part of the participants will make a big difference in the trial results. Both differential and similar dropout rates across trial arms may engender the comparability of groups, and high attrition rate also limits the interpretation of trial results [20].

Factors relating to patient compliance are multifaceted, but sociopyschological studies have suggested that values underpin patient behaviors in a clinical study. When it comes to what kind of values turn out to compliance and what to poor compliance, a review [6] of factors from the patient's perspective gave us some hints.

In summary, good compliance has been found to be connected with the following patient values:

(a) feeling susceptible to a disease or its complications;

(b) believing the disease or complications may end up with severe consequences;

(c) believing in the efficacy or benefits of the treatment.

More items of values have been reported to relate to poor compliance behaviors, including the following:

(a) believing that long-term use of western medicine was harmful;

(b) worrying about diminished effectiveness of medication over time;

(c) fearing to develop dependence on long-term use of drug;

Table 1: Manifestations of patient values in each phase of a randomized controlled trial.

Phase	Circumstance A	Circumstance B	B's implications	Patient values' role	Manifestations
Enrollment	Gave informed consent including consent to randomization	Refused to give informed consent and did not admit	Delays of recruitment Reduced sample size	Made judgments	Choices
Randomization and intervention allocation	Agreed to receive allocated treatment	Randomized to an unopted treatment and refused to continue	Ended participation Decreased statistical power	Made judgments	Choices
		Attended preference controlled trials	Entered the opted group	Directed preferences	Preferences
Treatment duration	Received treatment as required	Received treatment not as required	Violation of protocols	Guided behaviors	Compliance
		Withdrew from treatment or participation	Withdrawals		
Followup	Reported outcomes			Made judgments	Patient reported outcomes
	Completed all visits as required	Missed visits	Violation of protocols	Guided behaviors	Compliance
		Withdrew from the trial	Lost to followup		
	Reported outcomes			Made judgments	Patient reported outcomes

(d) perceiving less need for drug as disease is God's will and is uncontrollable;

(e) having low motivation to change behaviors or take medication;

(f) having negative attitudes or even depression;

(g) feeling stigmatized while on medication.

Some of the above values apply well to patients attending clinical trials with TCM. Generally speaking, TCM regimens applied in clinical research feature a long duration of treatment, slow onset of action, and enduring course of effects. In trials testing Chinese patent medicine for chronic stable coronary artery disease, for example, the participants may be highly motivated at the beginning, but their patience could be toiled by the long treatment duration (usually lasting for months in addition to a 1-year follow-up period), and they may feel disappointed if the treatment effects are less prominent than expected. They may also feel good about their health after weeks of treatment and begin to take fewer drugs or even miss treatment sessions by their own free will. Along with disappointment, fulfillment of expectations, and other negative or positive experiences with the therapy in a TCM trial, a variety of new beliefs and personal codes of conduct might be formed. Many of these could lead to good or poor compliance. However, patients' psychological changes predictive of nonadherence are subtle and hardly perceptible, thus, posing challenges to the trialists.

Many methods and techniques have been developed to monitor and manage the noncompliance phenomenon, but few of them were based on the patients' needs and values. Here, we propose the use of in-depth physician-doctor communication during or after each treatment session (e.g., during acupuncture sessions) to detect possible predicators of any non-compliance behavior so that the trialists can take measures accordingly. For instance, the participants could be clearly informed of the potential health hazards that resulted from irregular or discontinued treatment and of the benefits of adherence to the treatment regimen. More physician attention, and social support, perhaps also financial help should be extended to all participants to prevent them from feeling depressed, isolated, or utilized. This approach could also be part of the qualitative research projects nested within TCM clinical trials for deepening understanding on patient experiences with complex interventions, as proposed by Liu [21].

Empirical evidence from clinical research in TCM showed that an emphasis on the improvement of patient-important outcomes, rather than laboratory indicators, could be more attractive to the patients and therefore such study design could have a better profile of participant retention. In a randomized trial testing the superiority of alendronate sodium tablets plus acupuncture over alendronate sodium tablets for osteoporosis, the former group had a dropout rate of 72% compared with 32% of the latter group over a 12-month treatment period, and with statistically significant differences ($P < 0.05$) [22]. The main reason is that the acupuncture sessions provided extra pain relief for patients in the treatment arm (reduction in VAS scores, $P < 0.05$).

And for patients suffering from osteoporosis, alleviation of pain counts a lot.

3.4. Patient-Reported Outcomes. The patient-reported outcome (PRO) is an umbrella term for all patient assessments of a health condition and its treatment [23]. By definition, it relies heavily on the subjective perceptions of the patient himself and therefore captures well his experiences and perspectives [23], reveals what matters and what does not to him [24], and constitutes part of the representations of personal values. During data collection (in the treatment duration or during followups), patients might be required to complete items in a PRO instrument, describing changes of symptoms, health functioning, and sense of wellbeing or reporting on the perceived efficacy, safety, and acceptability of the treatment. Process evaluation such as patient reported satisfaction and compliance is another dimension of the PRO instrument. While medical studies increasingly crave the humanistic feature, PROs are winning places in both clinical trials and drug approvals in the TCM field.

A successful PRO instrument is the product of systematic item collection, rigorous psychometrics verification, and revisions from repeated pilot surveys, which satisfies certain development, psychometric and scaling standards. A PRO tool for TCM also incorporates many aspects that are characteristics of the Chinese medicine, such as the introduction of measurement items relating to the human constitution, the unity of physical and mental health, and the balance between the person and the nature. Moreover, items concerning signs and symptoms relevant to TCM pattern diagnosis are given prominence in a PRO instrument for TCM, such as the sense of taste, sleep pattern, energy and sound, and status of urine and stool. Most importantly, the construction of such a PRO follows a conceptual framework guided by the TCM theories [25]. As Liu noted, "the application of PRO instruments in TCM could be a large step towards the scientific and standardized efficacy evaluation of TCM" [26].

4. Discussion

It seems that patients have values and the manifestations of these values tend to be ubiquitous in clinical trials with TCM (see Table 1 for a summary of these manifestations). They either turn out to behaviors that impede the progress of a RCT or those that facilitate it. To manage these desirable and undesirable humanistic features of clinical studies, patient-friendly trial design and convenience-for-patients measures are recommended. Preference controlled trials that allow the participant to choose from available treatment options of one's own free will, the introduction of patient-reported outcomes that matter to the participants, and other innovative measures fostering convenience of participation could provide valuable references for future trialists. Furthermore, there is more we can do to improve the quality of clinical research in TCM now that we know what kind of patient values may pose what type of risk of bias in every stage of the trial. Initiatives shall be taken to weaken negative influences by guiding patient values. It is time to confront the challenge and do something.

5. Conclusions

Patient values and the various manifestations tend to have wide implications for clinical research in TCM. It is recommended that trialists respect these values, use participant-friendly design and patient-reported outcomes, take convenience-for-patients measures, and help foster rational beliefs and behaviors of the participants in future clinical trials with TCM.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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References

[1] S. E. Straus, W. S. Richardson, P. Glasziou P, and R. B. Haynes, *Evidence-Based Medicine: How to Practice and Teach EBM*, 3rd edition, 2005.

[2] J. L. Wang, *Clinical Epidemiology: Design, Measurement and Evaluation in Clinical Study*, Shanghai Science and Technology Press, Shanghai, China, 3rd edition, 2009.

[3] P. R. Orr, D. W. Blackhurst, and B. S. Hawkins, "Patient and clinic factors predictive of missed visits and inactive status in a multicenter clinical trial," *Controlled Clinical Trials*, vol. 13, no. 1, pp. 40–49, 1992.

[4] S. Ross, A. Grant, C. Counsell, W. Gillespie, I. Russell, and R. Prescott, "Barriers to participation in randomised controlled trials: a systematic review," *Journal of Clinical Epidemiology*, vol. 52, no. 12, pp. 1143–1156, 1999.

[5] D. L. Sackett, "Introduction," in *Compliance With Therapeutic Regimens*, D. L. Sackett and R. B. Haynes, Eds., Johns Hopkins University Press, Baltimore, Md, USA, 1976.

[6] J. Lin, G. E. Sklar, V. M. S. Oh, and S. C. Li, "Factors affecting therapeutic compliance: a review from the patient's perspective," *Therapeutics and Clinical Risk Management*, vol. 4, no. 1, pp. 269–286, 2008.

[7] Y. Wei, J. Y. Yuan, S. Z. Wu et al., "A survey on the potential candidates'willingness and motive to participate in clinical studies in China," in *Proceedings of the 13th National Conference on Clinical Pharmacology*, Sichuan, China, 2012.

[8] M. King, I. Nazareth, F. Lampe et al., "Impact of participant and physician intervention preferences on randomized trials: a systematic review," *Journal of the American Medical Association*, vol. 293, no. 9, pp. 1089–1099, 2005.

[9] K. F. Schulz and D. A. Grimes, *The Lancet Handbook of Essential Concepts in Clinical Research*, Elsevier, 2006.

[10] D. J. Torgerson and B. Sibbald, "Understanding controlled trials: what is a patient preference trial?" *British Medical Journal*, vol. 316, no. 7128, pp. 360–364, 1998.

[11] P. W. Corrigan and M. S. Salzer, "The conflict between random assignment and treatment preference: implications for internal

validity," *Evaluation and Program Planning*, vol. 26, no. 2, pp. 109–121, 2003.

[12] M. R. Janevic, N. K. Janz, J. A. Dodge et al., "The role of choice in health education intervention trials: a review and case study," *Social Science and Medicine*, vol. 56, no. 7, pp. 1581–1594, 2003.

[13] K. McPherson, A. R. Britton, and J. E. Wennberg, "Are randomized controlled trials controlled? Patient preferences and unblind trials," *Journal of the Royal Society of Medicine*, vol. 90, no. 12, pp. 652–656, 1997.

[14] Preference Collaborative Review Group, "Patients'preferences within randomised trials: systematic review and patient level meta-analysis," *British Medical Journal*, vol. 337, Article ID a1864, 2008.

[15] A. H. L. Floyd and A. Moyer, "Effects of participant preferences in unblinded randomized controlled trials," *Journal of Empirical Research on Human Research Ethics*, vol. 5, no. 2, pp. 81–93, 2010.

[16] G. Rücker, "A two-stage trial design for testing treatment, self-selection and treatment preference effects," *Statistics in Medicine*, vol. 8, no. 4, pp. 477–485, 1989.

[17] J. E. Wennberg, M. J. Barry, F. J. Fowler, and A. Mulley, "Outcomes research, PORTs, and health care reform," *Annals of the New York Academy of Sciences*, vol. 703, pp. 52–62, 1993.

[18] S. D. Halpern, "Evaluating preference effects in partially unblinded, randomized clinical trials," *Journal of Clinical Epidemiology*, vol. 56, no. 2, pp. 109–115, 2003.

[19] C. R. Brewin and C. Bradley, "Patient preferences and randomised clinical trials," *British Medical Journal*, vol. 299, no. 6694, pp. 313–315, 1989.

[20] M. L. Bell, M. G. Kenward, D. L. Fairclough, and N. J. Horton, "Differential dropout and bias in randomised controlled trials: when it matters and when it may not," *British Medical Journal*, vol. 346, Article ID e8668, 2012.

[21] J. P. Liu, *Qualitative Research Methodology in Evidence-Based Chinese Medicine*, People's Public Health Publishing House, Beijing, China, 2009.

[22] X. Y. Zhao, S. Wu, and P. Wang, "Acupuncture for osteoporosis and the extra implications for compliance," *Journal of New Chinese Medicine*, vol. 45, no. 6, pp. 117–118, 2013.

[23] D. Patrick, "Concept of health-related quality of life and of patient-reported outcomes," in *Health-Related Quality of Life and Patient-Reported Outcomes: Scientific and Useful Outcome Criteria*, O. Chassany and C. Caulin, Eds., Springer, 2002.

[24] J. F. Fries, B. Bruce, and D. Cella, "The promise of PROMIS: using item response theory to improve assessment of patient-reported outcomes," *Clinical and Experimental Rheumatology*, vol. 23, supplement 39, no. 5, pp. S53–S57, 2005.

[25] Z.-K. Hou, F.-B. Liu, Y.-Y. Liang, K.-H. Zhuang, C.-H. Lin, and L.-J. Li, "On the necessity of developing quality of life instruments in traditional Chinese medicine," *Journal of Chinese Integrative Medicine*, vol. 9, no. 5, pp. 468–482, 2011.

[26] B. Y. Liu, *Measurement of Patient-Reported Outcomes: Concepts, Methods and Application*, People's Public Health Publishing House, Beijing, China, 2011.

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Research Article

Clinical Study on the Prevention of Oxaliplatin-Induced Neurotoxicity with Guilongtongluofang: Results of a Randomized, Double-Blind, Placebo-Controlled Trial

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Objective. Oxaliplatin-induced peripheral neurotoxicity continues to be a kind of frequent dose-limiting toxicity for many cancer patients. This study evaluated the preventive effects of Guilongtongluofang on peripheral neurotoxicity induced by oxaliplatin in patients with colorectal tumor. *Patients and Methods*. From May 2007 to May 2011, we conducted a randomized, double-blind, placebo-controlled trial. 120 patients of colorectal cancer treated with adjuvant oxaliplatin-based chemotherapy were randomly enrolled into the trial group and the control group. The trial group received Guilongtongluofang (at a dose of 200 mL once a day) from 3 days prior to chemotherapy. The control group received a placebo from 3 days prior to chemotherapy. Every 2-week cycle, neurotoxicity was evaluated using numeric rating scale for pain intensity and experienced relief. The primary endpoint was efficacy measurement which included oxaliplatin-induced neurotoxicity and tumor response. The differences of side effects between the two groups were also analyzed. *Results*. The percentage of grades 1-2 neurotoxicity was significantly lower in the trial group than that in the control group (13.3% versus 20.0%; $P < 0.05$) after two cycles of treatment. The difference of the percentage of neurotoxicity between the two groups was significant after six cycles (51.7% versus 70.0%; $P < 0.05$). Significant difference for the mean time to the development of grade 1+ neurotoxicity was found between the two groups (9.4 w in the trial group versus 6.5 w in the control group, $P < 0.05$). The cumulative incidence of grade 1 or more sensory neurotoxicity was significantly lower in the trial group than that in the control group ($P < 0.05$). No significant differences of tumor response rate were found between the two groups the trial group and the control group. No significant difference was found between the trial group and the control group (all $P > 0.05$). *Conclusion*. This study provides evidence that Guilongtongluofang is a promising drug for the prevention of oxaliplatin-induced neurotoxicity in patients with colorectal cancer, and it does not reduce the efficacy of oxaliplatin.

1. Introduction

Oxaliplatin is the third-generation platinum-based anticancer drug and is a useful drug in colorectal cancer therapy. Especially, oxaliplatin combined with 5-fluorouracil(5FU)/leucovorin (FOLFOX) has emerged as the standard of care in adjuvant treatment and in first-line and second-line therapy of advanced-stage colorectal cancer [1, 2]. Its overall safety profile is good, but neurotoxicity is the main adverse effect and is a kind of dose-limiting toxicity. It often leads to chemotherapeutic dosage reduction, treatment delay, and treatment discontinuation [2, 3], even when the patient is still responding to the drug.

Oxaliplatin-induced neurotoxicity can be divided into two distinct syndromes. The first one is a unique syndrome of acute, transient peripheral nerve hyperexcitability, which

is unique among the platinum complexes studied to date [4]. Patients may experience cold-sensitive paresthesias and dysesthesias of the hands and feet, as well as larynx and jaw. This kind of neurotoxicity usually occurs shortly after the infusion of oxaliplatin and at low total cumulative dose. Acute neurotoxicity occurs frequently, with the incidence varying from 81.5% to 98%, and is often induced by cold exposure [5]. It is always reversible and does not require discontinuation of therapy. The second syndrome is a peripheral sensory neurotoxicity occurring mainly in the distal extremities with symptoms similar to those caused by cisplatin. Development of this syndrome is related to the cumulative dose, generally becoming a clinical problem when the cumulative dose approximates 800 mg/m^2. It is reversible, but it may last for several months and lead to discontinuation of treatment [6, 7].

Several strategies have been proposed to prevent or treat oxaliplatin-induced neurotoxicity, such as gabapentin, calcium-magnesium infusions, antiepileptic drugs like carbamazepine, amifostine, and glutathione. However, there were no randomized trials which had demonstrated a prophylactic or therapeutic effect of these agents on oxaliplatin cumulative neurotoxicity. Guilongtongluofang, a traditional Chinese medicine, is composed of ramulus cinnamomi, radix astragali, earthworm, safflower, radix angelicae sinensis, ligusticum, spatholobus, radix paeoniae alba, rhizoma curcumae, and licorice. All the herbs added increased the function of warming and activating yang to promote blood circulation to relieve from symptoms such as numbness and cold sensation in patients.

We hypothesized that Guilongtongluofang might have effect on the prevention of oxaliplatin-induced neurotoxicity. This study was therefore designed to determine the preventive effects of Guilongtongluofang on peripheral neurotoxicity induced by oxaliplatin in patients with colorectal tumor.

2. Materials and Methods

2.1. Plant Material and Preparation of the Extract. The plant material was purchased from the Beijing Medicinal Material Company (Beijing, China). Guilongtongluofang was composed of ramulus cinnamomi 9 g, earthworm 12 g, radix astragali 30 g, safflower 10 g, radix angelicae sinensis 12 g, ligusticum 12 g, spatholobus 30 g, radix paeoniae alba 30 g, rhizoma curcumae 9 g, and licorice 6 g. The aqueous extract was prepared by the following processes: each dose of the dried herbs was twice decocted in water to 100 mL, and then the 200 mL was mixed and divided into two potions to be taken twice daily.

2.2. Patient Population. Consecutive patients with colon or rectum cancer were enrolled in this prospective study from the chemotherapy department of Weifang Hospital of Traditional Chinese Medicine during the period from May 2007 to May 2011. Criteria for enrollment include (1) ≥18 years of age; (2) Eastern Cooperative Oncology Group performance status of 0 to 2; (3) normal bone marrow function (leukocyte count > 4,000/L, platelet count > 100,000/L), liver function (serum bilirubin < 1.5 mg/dL), renal function (creatinine < 1.5 mg/dL), and cardiac function (stable heart rhythm, no active angina, and no clinical evidence of congestive heart failure); (4) life expectancy ≥ 6 months; (5) no preexisting peripheral neurotoxicity from any cause. Pregnant or nursing women were not eligible for this study. Patients with diabetic neuropathy were also excluded. Concomitant use of anticoagulants, platelet aggregation inhibitors, opioids, anticonvulsants, tricyclic antidepressants, and other neuropathic pain medication agents was also prohibited. Informed consent was obtained from all participants, and this study was approved by the local ethics committee.

Using a prospective, randomized, placebo-controlled, double-blind design, 120 patients were randomly assigned into the trial group (60 patients) and the control group (60 patients). There are 83 males and 37 females, with a median age of 52.5 years. Group assignment for all subjects was determined using a random table prior to initiation of the study. The sequence of assignments was unknown to any of the investigators. Each assignment was kept in a sealed envelope, and the order in numeric number was shown on the outside of the envelope. Thus, the orders could not be changed. Envelopes were arranged in order. The principal investigator generated this random selection a few months before recruiting the first subject. No significant differences in gender, age, physical condition, and clinical stage of disease between the two groups were found.

2.3. Treatment. All of the patients were given FOLFOX4 chemotherapy for six cycles. The chemotherapeutic regimen consisted of oxaliplatin 85 mg/m^2 on day 1, given as a 3-hour infusion in 250 mL of dextrose 5%, concurrent with 6-S-stereoisomer of leucovorin 200 mg/m^2 as a 2-hour infusion followed by fluorouracil 400 mg/m^2 and 24-hour infusion of fluorouracil 2400 mg/m^2/d for 2 consecutive days. Then, two weeks later, the patients were given the same chemotherapeutic regimen for 2 consecutive days again. Patients who finished twice chemotherapeutic regimen were defined as one cycle.

The trial group was given Guilongtongluofang from 3 days prior every chemotherapy and the herb treatment was administered for consecutive 10 days. One dose of Guilongtongluofang was taken every day. The control group was given placebo seen as Guilongtongluofang in the same way.

2.4. Study Endpoints. The primary study endpoint was efficient measurement which included oxaliplatin-induced neurotoxicity and tumor response.

Oxaliplatin-induced neurotoxicity was assessed after every two cycles using the National Cancer Institute's (NCI) common toxicity criteria (CTC) as follows: grade 1: paresthesia and/or dysesthesia (induced by cold) with complete regression within one week; grade 2: paresthesia and/or dysesthesia with complete regression within 14 days; grade 3: paresthesia and/or dysesthesia with incomplete regression at day 14; grade 4: paresthesia and/or dysesthesia with functional consequences [8]. Complete neurological examinations were performed at baseline and after two, four,

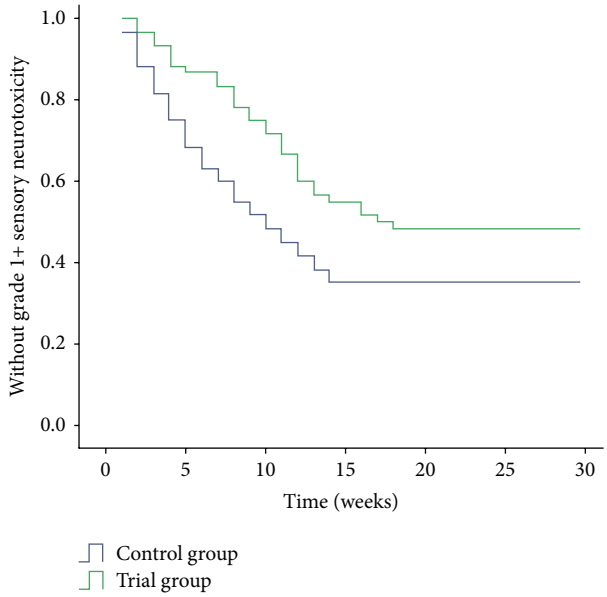

Figure 1: Time to grade 1 or more sensory neurotoxicity in patients treated with or without Guilongtongluofang.

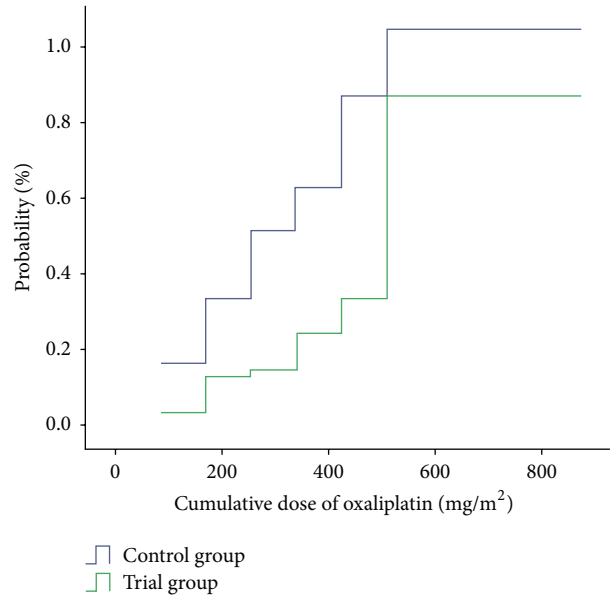

Figure 2: Probability of sensory neurotoxicity by cumulative dose of oxaliplatin in patients treated with or without Guilongtongluofang.

and six cycles of treatment, respectively. An experienced neurologist evaluated the data to assess possible between-group differences in electrophysiological function.

Treatment response was assessed according to World Health Organization criteria based on a CT scan 2 months after the completion of treatment. A complete response was defined as the disappearance of all known disease for at least 4 weeks. A partial response required a reduction of at least 50% in the size of the tumor for at least 4 weeks. Progressive disease was defined as an increase of 25% or more in the size of the tumor, and stable disease was defined as no change or less than 50% reduction or more than 25% increase.

The secondary endpoint was safety, and the number of participants discontinued to treatment. All patients underwent followup office visits every two weeks until 2 months after the completion of treatment. At each followup, blood routine, transaminases, blood urea nitrogen (BUN), and creatinine were measured, and the incidence and severity of various side effects (i.e., diarrhea, nausea, vomiting, headache, dizziness and abdominal pain, etc.) which may be associated with treatment were monitored.

2.5. Statistical Analysis. With the published event rates for our primary endpoint, we estimated the number of subjects required for the study to have >80% power ($\alpha = 0.05$) to detect an absolute 30% reduction in the incidence of the endpoint. Continuous data were expressed as mean ± SD, and discrete data were given as counts and percentages. Pearson Chi-square test was used to compare categorical variables and the difference of percentage (rate) of neurotoxicity. Proportion of patients with grade 1 to grade 4 neurotoxicity was also compared with a two-sided Fisher's exact test. All data were analyzed using SPSS version 17.0 for windows. Any P value given is two sided and subjects to a local significant level of 5%.

3. Results

3.1. Patient Characteristics. Patient characteristics are shown in Table 1. There were no significant between-group differences in age, gender, performance status, location of primary tumor, histological differentiation, and sites of distant metastasis. All the patients completed at least six treating cycles and were qualified for analysis. There were no drop-out cases.

3.2. Oxaliplatin-Induced Neurotoxicity. As shown in Table 2, after two cycles of treatment, 8 patients in the trial group and 11 patients in the control group had grades 1-2 neurotoxicity, the percentage of neurotoxicity was significantly lower in the trial group than that in the control group (13.3% versus 20.0%; $P < 0.05$). After four cycles, 14 (23.3%) patients in the trial group and 18 (30.0%) patients in the control group experienced grades 1-2 neurotoxicity. The difference of the percentage of neurotoxicity between the two groups was nearly significant after four cycles of treatment (28.3% versus 43.3%; $P = 0.05$) and significant after six cycles (51.7% versus 70.0%; $P < 0.05$).

In addition, the onset of grade 1 or more sensory neurotoxicity was much later in patients who received Guilongtongluofang. Data regarding the time to grade 1+ sensory neurotoxicity are illustrated in Figure 1. Significant difference for the mean time to the development of grade 1+ neurotoxicity was found between the two groups (9.4 w in the trial group versus 6.5 w in the control group, $P < 0.05$).

The incidence of grade 1 or more sensory neurotoxicity increased with the increasing cumulative dose of oxaliplatin (Figure 2). The cumulative incidence of grade 1 or more

Table 1: Basic characteristics of study population.

Characteristics	Trial group (n, %) ($n = 60$)	Control group (n, %) ($n = 60$)	P value
Age (years)			
≥50	10 (16.7)	7 (11.7)	0.83
<50	50 (83.3)	53 (88.3)	
Gender			
Male	43 (71.7)	40 (66.7)	0.55
Female	17 (28.3)	20 (33.3)	
Performance status			
0	34 (56.7)	29 (48.3)	0.36
1,2	26 (43.3)	31 (51.7)	
Location of primary tumor			
Colon	32 (53.3)	34 (56.7)	0.74
Rectum	28 (46.7)	26 (43.3)	
Histological differentiation			
Well/moderately	45 (75.0)	41 (68.3)	0.41
Poorly/unknown	15 (25.0)	19 (31.7)	
Sites of distant metastasis			
Liver	12 (20.0)	10 (16.7)	
Lung	8 (13.3)	8 (13.3)	0.74
Liver and lung	4 (6.7)	3 (5.0)	
Others	0	1 (1.7)	

Table 2: Incidence of oxaliplatin-induced neurotoxicity in the trial group and the control group.

Neurotoxicity	Trial group (n, %) ($n = 60$)	Control group (n, %) ($n = 60$)	P value
After two cycles			
Grade 0	52 (86.7)	48 (80.0)	
Grades 1-2	8 (13.3)	11 (18.3)	0.04
Grades 3-4	0 (0.0)	1 (1.7)	
After four cycles			
Grade 0	43 (71.7)	34 (56.7)	
Grades 1-2	14 (23.3)	18 (30.0)	0.05
Grades 3-4	3 (5.0)	8 (13.3)	
After six cycles			
Grade 0	29 (48.3)	18 (30.0)	
Grades 1-2	24 (40.0)	23 (38.3)	0.04
Grades 3-4	7 (11.7)	19 (31.7)	

sensory neurotoxicity was significantly lower in the trial group than that in the control group ($P < 0.05$). The median cumulative oxaliplatin doses are 510 mg in the trial group and 255 mg in the control group, respectively.

3.3. Tumor Response. All patients completed six cycles of treatment, and the overall response rates (complete response and partial response) were 43.3% in the trial group and 35.0% in the control group, respectively. Two patients in the trial group and two patients in the control group had a complete response, respectively. No significant differences of tumor response rate were found between the two groups (Table 3).

3.4. Adverse Events. Nonneurologic adverse events which may be associated with the treatment are listed in Table 4. No

Table 3: Objective tumor response in the trial group and the control group.

Group	n	CR (%)	PR (%)	SD (%)	PG (%)	P value
Trial group	60	2 (3.3)	24 (40.0)	28 (46.7)	6 (10)	0.72
Control group	60	2 (3.3)	19 (31.7)	32 (53.3)	7 (11.7)	

CR: complete response; PR: partial response; SD: stable disease; PG: progression.

Table 4: Adverse events in the trial group and the control group.

Adverse events	Trial group (n, %) ($n = 60$)	Control group (n, %) ($n = 60$)	P value
Anemia			
Grades 1-2	7 (11.7)	8 (13.3)	0.78
Grades 3-4	0	0	
Neutropenia			
Grades 1-2	14 (23.3)	13 (21.7)	0.92
Grades 3-4	7 (11.7)	6 (10.0)	
Thrombocytopenia			
Grades 1-2	10 (16.7)	9 (15.0)	0.80
Grades 3-4	0	0	
Nausea			
Grades 1-2	18 (30.0)	20 (33.3)	0.69
Grades 3-4	0	0	
Vomiting			
Grades 1-2	14 (23.3)	16 (26.7)	0.67
Grades 3-4	0	0	
Diarrhea			
Grades 1-2	12 (20.0)	13 (21.7)	0.56
Grades 3-4	1 (1.7)	3 (5.0)	
Stomatitis			
Grades 1-2	12 (20.0)	11 (18.3)	0.81
Grades 3-4	0	0	

significant difference was found between the trial group and the control group (all $P > 0.05$).

4. Discussion

Oxaliplatin has become an integral component of chemotherapeutic regimens for the treatment of colon or rectum cancer [9, 10]. Neurotoxicity is the most severe and dose-limiting cumulative toxicity resulting from oxaliplatin therapy [11]. The main neurotoxicity was cold-induced paresthesia after the use of oxaliplatin, which included hyperesthesia, chill, numbness of the hands and feet, electrified sensation, formication, foreign body sensation, and pain that might be exacerbated by exposure to cold.

The main target organ of platinum-based preparations with peripheral neurotoxicity is the dorsal root ganglion, which is consistent with the platinum accumulation studies [12]. The cause of neurotoxicity induced by oxaliplatin is still poorly understood, as demonstrated by the lack of efficacy of the various agents listed previously [13]; therefore, many other theories and drugs are currently being explored. One theory is the connection between free radicals and chemotherapy as a possible cause of neurotoxicity. Free radicals are highly reactive compounds with one or more unpaired electron. Some other neuromodulatory agents have already been tested in patients with oxaliplatin-induced neurosensory toxicity. In a pilot, single-arm study, calcium gluconate, and magnesium sulfate infusions, prior and after oxaliplatin, seemed to be active against acute symptoms [14]. Unfortunately, the prospective evaluation of this treatment was interrupted because of a lower tumor response rate in the Ca/Mg arm [15]. Other studies have proved that Ca/Mg salts could decrease the incidence of oxaliplatin-induced acute and cumulative neurotoxicity and thus enhance patients' tolerance to oxaliplatin, without significantly altering the efficacy of chemotherapy [16, 17].

In this study, we also proved the effects of Guilongtongluofang on preventing acute and chronic oxaliplatin-induced neurotoxicity. 8 patients in the trial group and 11 patients in the control group appeared grades 1-2 neurotoxicity after two

cycles of chemotherapy. After four cycles, and especially six cycles oxaliplatin-induced neurotoxicity gradually increased with increasing dose. It showed that the neurotoxicity was dose-dependent. After four cycles, 14 patients (23.3%) in the trial group and 18 patients (30.0%) in the control group experienced grades 1-2 sensory neurotoxicity. The difference of the incidence of neurotoxicity between the two groups was significantly different after six cycles of treatment. As for tumor response, the response rate was 43.3% in the trial group and 35.0% in the control group, no significant difference was found between the two groups.

Most scholars considered [18] that the platinum concentrations are greater in the dorsal root ganglion followed by dorsal root and peripheral nerves. The accumulation of oxaliplatin or metabolites oxalate in the dorsal root ganglion is attributed to increasing the outflow and slowing in-flow of Na^+, so it increases the negative values of the membrane potential and weakens action potential, leading to high sensitivity and excitability of the peripheral nerve. Oxaliplatin can also adjust apoptosis and the balance of cell cycle. It can interact with mitochondrial DNA, lead to oxidative stress, and increase p53 activity and mitochondrial release of cytocrome-c pathway, independent of Fas receptor activation, as well as activation of p38 and ERK1/2 [19]. Scuteri et al. [20] found that the validity of MAPKs is the target of neuroprotective therapies during chemotherapeutic treatment. One method of avoiding oxaliplatin-induced neurotoxicity is kept away from cold drinks and cold objects. Clinicians should also pay close attention to the oxaliplatin cumulative dose and dosing interval. Patients affected are usually those who received doses $\geq 540\ mg/m^2$ or over 4 cycles of therapy [21].

According to the modern pharmacological research, the main component of *Astragalus* are amino acids, flavonoids, and trace elements, which cannot only improve cell tolerance to hypoxia, antioxidant capacity, and scavenging free radical but also dilate blood vessels, improve the blood supply of cardiac muscle, and reduce the viscosity of blood [22, 23]. It is also useful to resist tumor and improve immunity [24]. Earthworm, safflower, and chuanxiong can dilate the blood vessels, improve microcirculation and blood flow, inhibit platelet aggregation, and prevent thrombosis [25]. Ramulus cinnamomi and radix paeoniae alba are useful in dilating blood vessels and promoting and adjusting blood circulation [26]. Rhizoma curcumae is used for invigorating Qi to dissipate blood stasis and relieve pain [27]. All the herbs together can increase the function of warming Yang, flowing Qi, and activating blood circulation by benefiting vital energy and nourishing blood. All these above bring about dissipating blood stasis to dredge the collateral, detoxicating and resolving stagnation of pathogens and activating blood circulation to dissipate blood stasis. Thus, Guilongtongluofang has the function of activating blood circulation and repairing nerve injury, which leads to the prevention of peripheral neurotoxicity.

There are some limitations in our study. First, all patients underwent follow-up office visits every two weeks until 2 months after the completion of treatment, and hence a long-term study is obviously needed to further confirm our results. Second, clinical findings were used as the endpoints in our study, whereas a hard clinical endpoint such as mortality should be used in a large sample of patients in a future study.

In summary, the application of FOLFOX4 treatment with Guilongtongluofang in advanced colorectal cancer cannot only reduce the incidence of neurotoxicity but also improve the quality of life in patients. It does not reduce the efficacy of the treatment or increase the toxicity of chemotherapy.

5. Conclusion

Guilongtongluofang can safely decrease the incidence of severe neurotoxicity induced by FOLFOX4 regimen, without reducing the efficacy of the treatment or increasing the side effects. Therefore, Guilongtongluofang is useful in preventing oxaliplatin-induced neurotoxicity in patients with colorectal cancer.

Conflict of Interests

There is no conflict of interests regarding the publication of this paper.

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References

[1] A. de Gramont, A. Figer, M. Seymour et al., "Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer," *Journal of Clinical Oncology*, vol. 18, no. 16, pp. 2938–2947, 2000.

[2] S. Giacchetti, B. Perpoint, R. Zidani et al., "Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer," *Journal of Clinical Oncology*, vol. 18, no. 1, pp. 136–147, 2000.

[3] M. A. Khattak, "Calcium and magnesium prophylaxis for oxaliplatin-related neurotoxicity: is it a trade-off between drug efficacy and toxicity?" *Oncologist*, vol. 16, no. 12, pp. 1780–1783, 2011.

[4] R. H. Wilson, T. Lehky, R. R. Thomas, M. G. Quinn, M. K. Floeter, and J. L. Grem, "Acute oxaliplatin-induced peripheral nerve hyperexcitability," *Journal of Clinical Oncology*, vol. 20, no. 7, pp. 1767–1774, 2002.

[5] R. J. Cersosimo, "Oxaliplatin-associated neuropathy: a review," *Annals of Pharmacotherapy*, vol. 39, no. 1, pp. 128–135, 2005.

[6] S. Cascinu, V. Catalano, L. Cordella et al., "Neuroprotective effect of reduced glutathione on oxaliplatin-based chemotherapy in advanced colorectal cancer: a randomized, double-blind, placebo-controlled trial," *Journal of Clinical Oncology*, vol. 20, no. 16, pp. 3478–3483, 2002.

[7] S. R. Land, J. A. Kopec, R. S. Cecchini et al., "Neurotoxicity from oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: NSABP C-07," *Journal of Clinical Oncology*, vol. 25, no. 16, pp. 2205–2211, 2007.

[8] *NCI Common Toxicity Criteria, Version 2. 0*, National Institutes of Health, National Cancer Institute, Washington, DC, USA, 1998.

[9] T. André, C. Boni, L. Mounedji-Boudiaf et al., "Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer," *The New England Journal of Medicine*, vol. 350, no. 23, pp. 2343–2351, 2004.

[10] S. R. Alberts, W. L. Horvath, W. C. Sternfeld et al., "Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a North Central Cancer Treatment Group phase II study," *Journal of Clinical Oncology*, vol. 23, no. 36, pp. 9243–9249, 2005.

[11] H. Hochster, A. Chachoua, J. Speyer, J. Escalon, A. Zeleniuch-Jacquotte, and F. Muggia, "Oxaliplatin with weekly bolus fluorouracil and low-dose leucovorin as first-line therapy for patients with colorectal cancer," *Journal of Clinical Oncology*, vol. 21, no. 14, pp. 2703–2707, 2003.

[12] C. Meijer, E. G. E. de Vries, P. Marmiroli, G. Tredici, L. Frattola, and G. Cavaletti, "Cisplatin-induced DNA-platination in experimental dorsal root ganglia neuronopathy," *NeuroToxicology*, vol. 20, no. 6, pp. 883–887, 1999.

[13] L. A. Kottschade, J. A. Sloan, M. A. Mazurczak et al., "The use of vitamin E for the prevention of chemotherapy-induced peripheral neuropathy: results of a randomized phase III clinical trial," *Supportive Care in Cancer*, vol. 19, no. 11, pp. 1769–1777, 2011.

[14] L. Gamelin, M. Boisdron-Celle, R. Delva et al., "Prevention of oxaliplatin-related neurotoxicity by calcium and magnesium infusions: a retrospective study of 161 patients receiving oxaliplatin combined with 5-fluorouracil and leucovorin for advanced colorectal cancer," *Clinical Cancer Research*, vol. 10, no. 12, part 1, pp. 4055–4061, 2004.

[15] Y. Tatsushima, N. Egashira, Y. Narishige et al., "Calcium channel blockers reduce oxaliplatin-induced acute neuropathy: a retrospective study of 69 male patients receiving modified FOLFOX6 therapy," *Biomedicine & Pharmacotherapy*, vol. 67, no. 1, pp. 39–42, 2013.

[16] A. Grothey, D. A. Nikcevich, J. A. Sloan et al., "Intravenous calcium and magnesium for oxaliplatin-induced sensory neurotoxicity in adjuvant colon cancer: NCCTG N04C7," *Journal of Clinical Oncology*, vol. 29, no. 4, pp. 421–427, 2011.

[17] F. Wen, ZhouY, W. Wang et al., "Ca/Mg infusions for the prevention of oxaliplatin-related neurotoxicity in patients with colorectal cancer: a meta-analysis," *Annals of Oncology*, vol. 24, no. 1, pp. 171–178, 2013.

[18] A. A. Argyriou, J. Bruna, P. Marmiroli, and G. Cavaletti, "Chemotherapy-induced peripheral neurotoxicity (CIPN): an update," *Critical Reviews in Oncology/Hematology*, vol. 82, no. 1, pp. 51–77, 2012.

[19] W. Grisold, G. Cavaletti, and J. Windebank, "Peripheral neuropathies from chemotherapeutics and targeted agents: diagnosis, treatment, and prevention," *Neuro-Oncology*, vol. 14, supplement 4, pp. 45–54, 2012.

[20] A. Scuteri, A. Galimberti, M. Ravasi et al., "NGF protects dorsal root ganglion neurons from oxaliplatin by modulating JNK/Sapk and ERK1/2," *Neuroscience Letters*, vol. 486, no. 3, pp. 141–145, 2010.

[21] A. Hosokawa, K. Ogawa, T. Ando et al., "Preventive effect of traditional Japanese medicine on neurotoxicity of FOLFOX for metastatic colorectal cancer: a multicenter retrospective study," *Anticancer Research*, vol. 32, no. 7, pp. 2545–2550, 2012.

[22] Q. A. Zhang, X. H. Fan, Z. Q. Zhang et al., "Extraction, antioxidant capacity and identification of Semen Astragali Complanati (Astragalus complanatus R. Br.) phenolics," *Food Chemistry*, vol. 141, no. 2, pp. 1295–1300, 2013.

[23] Q. Zhang, W. Y. Gao, Y. Zhang et al., "Protective effects of astragalus extract against intermittent hypoxia-induced hippocampal neurons impairment in rats," *Chinese Medical Journal*, vol. 126, no. 8, pp. 1551–1554, 2013.

[24] J. Wang, X. Tong, P. Li, H. Cao, and W. Su, "Immunoenhancement effects of Shenqi Fuzheng Injection on cyclophosphamide-induced immunosuppression in Balb/c mice," *Journal of Ethnopharmacology*, vol. 139, no. 3, pp. 788–795, 2012.

[25] Y.-F. Zhu, H.-M. Luo, Z.-L. Deng, D.-Y. Fu, W. Yao, and J. Dai, "Effects of the Chinese patent medicine, Honghua injection, on platelet glycoprotein Tib/Ufa receptors in patients with acute coronary syndrome: a randomized controlled trial," *Journal of Chinese Integrative Medicine*, vol. 10, no. 3, pp. 318–323, 2012.

[26] Y. K. Koo, J. M. Kim, J. Y. Koo et al., "Platelet anti-aggregatory and blood anti-coagulant effects of compounds isolated from Paeonia lactiflora and Paeonia suffruticosa," *Pharmazie*, vol. 65, no. 8, pp. 624–628, 2010.

[27] J. Shi and P. K. Wei, "Professor Wei Pin-kang's experience in treating chemotherapy induced nausea and vomiting: an analysis of herbal medication," *Zhongguo Zhong Xi Yi Jie He Za Zhi*, vol. 32, no. 4, pp. 556–559, 2012.

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Review Article

Clinical Research of Traditional Chinese Medicine Needs to Develop Its Own System of Core Outcome Sets

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Currently, quality issues concerning clinical research of traditional Chinese medicine (TCM) have come into the spotlight. It has been recognized that poorly-devised research methodology largely restricted the development of clinical research in TCM. The choice of appropriate outcome measurements is key to the success of clinical research; however, the current procedure for outcomes selection in clinical research of TCM is problematic due to the underdevelopment of clinical methodology. Under this circumstance, we propose the introduction to the concept of Core Outcome Set (COS) and discuss the feasibility of developing a COS system that caters for clinical studies in TCM, in the hope that the outcome evaluation system could be up to international standards.

1. Introduction

Clinical effectiveness is not only important for traditional Chinese medicine (TCM), but for all medical systems. Clinical research in TCM has been developed relatively later. Largely due to the many existing methodological defects of TCM trials, the efficacy of TCM remains controversial [1, 2]. All these issues have created a bottleneck in the development of TCM. There is a growing recognition that more attention has been paid to enhance the quality in clinical research of TCM [3, 4]. Especially in this decade, a new discipline, clinical evaluation of TCM, has formed into being and its development has been supported by the Chinese Major Science and Technology Projects. Owing to concerted efforts from a panel of experts with multidisciplinary background, the quality of clinical research of TCM has been improved, in terms of the construction of clinical research platform and the introduction of process management. There have been several achievements, for instance, the construction and implementation of the central randomization system, the application of the clinical data management system, the introduction of ethical review and trial registration, the promotion of the Consolidated Standards of Reporting Trials (CONSORT) statement, and the standardization of the data processing and analysis techniques.

2. Problems with Outcome Measures in Clinical Trials of TCM

Consensus on regarding what constitute a good design has been reached by most scholars, except some characteristics of TCM which have unique difficulties, including placebo making, sham control of acupuncture, tailoring treatment principle, and diagnostic system. Outcome measure is one of the key factors. For example, a systematic review of 35 trials investigating the efficacy of TCM for chronic obstructive pulmonary diseases (COPD) reported a total of 22 different outcomes [5]. Another systematic review [6] including 17 randomized controlled trials (RCTs) with compound salvia dropping pills for unstable angina pectoris reported 11 outcome measures. Among all included studies, 11 studies (65%) reported angina improvement, 10 reported electrocardiogram improvement, and only one study reported the incidence of major cardiovascular events. 15 trials (88%) had a treatment duration of 4 weeks, too short to identify clinically significant improvement on angina. A systematic

review [7] of primary studies on a combination of TCM treatment regimens for improving the movement function of poststroke patients included 34 RCTs with 11 different outcome measures, all being intermediate outcomes. 29 (85%) RCTs reported total effective rate; however, the original data and the standard against which to judge efficacy were not found in the primary study. In 23 RCTs (85%), the treatment period lasted less than 30 days. Moreover, only one study reported adverse events.

Problems concerning the choice and reporting of outcome measures for clinical trials of TCM were summarized as follows [5, 8–10]. (1) Outcome measured and reported in clinical trials of the same condition varied greatly, and there was apparent selective reporting bias. (2) Soft outcome measures are often employed such as percentage of patients perceiving benefit. (3) Subjective outcome measures were in a dominant position while objective outcome measures were less frequently adopted. (4) Lack of agreed and standardized evaluation criteria for TCM-related outcomes (e.g., tongue and pulses). (5) Surrogate endpoints bearing limited importance to practitioners and patients, such as biochemical indicators, were widely adopted, whereas important endpoint outcomes were less frequently reported. (6) Insufficient attention has been paid to the reporting of adverse event and adverse drug reaction associated with the use of herbal medicines.

3. Origin and Development of a Core Outcome Set (COS)

Concerning the same health care issue, the prospective of the patients, clinicians, researchers, and policymakers may vary greatly. Lack of consideration of this issue will lead to study results with less practical value. Therefore, selecting appropriate outcome(s) is crucial in the design of clinical trials. In addition, the results of systematic reviews and meta-analysis are an important source of evidence for health-related decision making, and the credibility of these results are based on the validity and quality of primary studies. If there are defections in the design and reporting of individual trials, systematic reviews and meta-analysis will not generate reliable evidence. For instance, the results of several studies cannot be compared and combined as a result of heterogeneity across studies, thus leaving valuable information wasted and the quality of evidence less rigorous [11].

The minimum outcome set which should be measured in a clinical trial for a specific disease, namely, a core outcome set (COS) [12], is an effective way to solve the above issues. It can simplify the design of clinical trials, reduce the risk of selecting inappropriate outcomes and minimize outcome reporting bias [13]. More importantly, the use of COSs can reduce the heterogeneity of the reported outcomes between studies, so that the results of different trials can be compared and combined [14].

As early as the late 1870s, the World Health Organization (WHO) has put forward the notion of adopting standardized outcomes and has compiled a handbook [15]. Since 1992, the OMERACT (Outcome Measures for Rheumatology Clinical Trials) collaboration has been committed to advocate and develop the COSs for clinical trials in rheumatology [16] and has made significant contributions [17]. Since 2002, the IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials) group has started working on COSs in trials with treatment for pain [18]. To date, more than 50 organizations or groups devoted to COS have been founded, involving several conditions and diseases such as eczema [19] and wound [20].

The projects for establishing and promoting COSs is gradually underway in different areas; however, the work has not gained worldwide popularity. Internationally acknowledged COSs has been sparse and a general guideline for COSs development is lacking [21]. Hence, clinical methodologists have launched the COMET (Core Outcome Measures in Effectiveness Trials) Initiative [22].

As an international academic organization, the initiatives gathered experts from different areas who are interested in promoting the development of COSs. Its management group is composed of four well-known experts in methodological research, including professor Doug Altman from the Oxford University, Professor Mike Clarke (the former director of the UK Cochrane Center) from the Queen's University in Belfast, Professor Paula Williamson from the University of Liverpool, and Professor Jane Blazeby from the University of Bristol [23]. The first COMET meeting was held in Liverpool in 2010 with a total of 110 participants including clinical researchers, systematic reviewers, clinicians, editors, health care consumers, trial funders, policy makers, and trials registries and regulators. The experts reached a consensus that it was necessary and urgent to promote COMET, and the relevant work should be conducted immediately. In July 2011, the COMET group held the second meeting, emphasizing the importance of developing COSs and the coordination and integration of information from various areas of health care, as well as the need to promote the development and application of COSs [24]. The third meeting will focus on how to select, evaluate, and use measurement of core outcomes to further promote the progress of relevant work [25].

4. Why COSs in Clinical Trials of TCM Are Established?

The issues surrounding outcome measures in clinical trials of TCM have been discussed widely. However, the focus was on the method of categorization and the choice of expressions for the outcomes. What has also been emphasized is that the chosen outcomes should represent the characteristics of TCM, for example, outcome measurements relevant to the TCM syndrome and other soft endpoints [26]. The above ideas on constructing COSs in the field of TCM have not aroused sufficient attention. During the recent decade, clinical studies with TCM have mushroomed and the quality has also improved. However, the majority of these studies have been rejected for publication on leading international medical journals, and their findings also received few citations and little recognition. The lack of a uniform standard for selecting and reporting outcomes may be one of the factors devaluing the clinical research of TCM. As

a result, promoting methodological research on COSs and establishing COSs based on the unique features of TCM are good solutions. It can also improve the quality of clinical research of TCM and the practicability of study results.

Furthermore, the development of clinical methodology for TCM in China kept following international trends, rather than taking initiatives. For instance, the reporting standards of herbal interventions were established by a group of Canadian experts [27], and the reporting standards in clinical trials of acupuncture were set by a panel of western scholars [28]. Neither of them involved a TCM specialist. It is time to take initiatives in establishing COSs catering for TCM clinical research in order to facilitate the work of scientific and rational evaluation of clinical efficacy of TCM.

At the time when the development of COSs in clinical research has just been started internationally, TCM scholars shall seize the opportunity and devise key techniques and methods for establishing COSs for TCM clinical research. In this way our research methodology may meet international standards. And we believe the uniqueness of TCM can add to the variety and vitality and also expand the breadth and depth of international COS research.

5. The Feasibility of Establishing COS in Clinical Trials of TCM

The COMET initiative team, the OMERACT working group, and the WHO have conducted extensive research on the development and application of COSs and have accumulated valuable experiences. The practical knowledge of and experiences with organization and management of the COMET initiative team will be of particular value for the development of COSs in clinical research of TCM. The currently existing methodological guidelines can provide guidance on our work. With advances in clinical epidemiology and evidence-based medicine, the development of research methodology and its application in clinical studies of TCM have made encouraging progress. Several multidisciplinary research teams have been formed, including scholars specialized in TCM, clinical epidemiology, evidence-based medicine, clinical pharmacology, statistics, and bioinformatics. This provides the professional research team necessary for establishing COSs in clinical trials of TCM.

The detailed work will be done based on guidance on developing the COMET initiative. Firstly, several diseases on which TCM therapies have unique effects should be identified such as chronic noncommunicable diseases. Secondly, systematic reviews especially high-quality Cochrane reviews for these diseases will be selected to determine outcomes related to specific disease. Thirdly, information from patients and TCM clinicians will be collected by using consensus methods such as the Delphi technique. Finally, outcome measures from systematic reviews and the consensus will be integrated.

The development of COSs in the field of TCM research will help improve the design and conducting of TCM trials to international standards, thereby lending credibility to the results.

Conflict of Interests

The authors declared that there was no conflict of interests regarding the publication of this paper.

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References

[1] J. H. Zhang, H. C. Shang, and G. H. Dai, "Key points of protocol design on clinical therapeutic research of traditional Chinese medicine," *Chinese Journal of Integrated Traditional and Western Medicine*, vol. 27, no. 2, pp. 171–173, 2007.

[2] M. Y. Di and J. L. Tang, "Adaption and application of the four phase trials to traditional Chinese medicines," *Evidence-Based Complementary and Alternative Medicine*, vol. 2013, Article ID 128030, 10 pages, 2013.

[3] H. C. Shang and B. L. Zhang, "To improve the overall level of traditional Chinese medicine research by goverment leading and multiple participation," *Chinese Journal of Evidence-Based Medicine*, vol. 10, no. 6, pp. 640–641, 2010.

[4] H. C. Shang, B. L. Zhang, and Y. Y. Wang, "Clinical research of traditional Chinese medicine needs 'a breakthrough'," *Tianjin Journal of Traditional Chinese Medicine*, vol. 30, no. 1, pp. 4–5, 2013.

[5] M. H. Wang, J. S. Li, X. Q. Yu et al., "A systematic review of outcomes of randomized controlled trials about stable-stage of chronic obstructive pulmonary disease," *Chinese Journal of Gerontology*, vol. 31, no. 11, pp. 1943–1948, 2011.

[6] J. H. Zhang, H. C. Shang, X. M. Gao et al., "Compound salvia droplet pill, a traditional Chinese medicine, for the treatment of unstable angina pectoris: a systematic review," *Medical Science Monitor*, vol. 14, no. 1, pp. RA1–RA7, 2008.

[7] Z. Junhua, F. Menniti-Ippolito, G. Xiumei et al., "Complex traditional Chinese medicine for poststroke motor dysfunction: a systematic review," *Stroke*, vol. 40, no. 8, pp. 2797–2804, 2009.

[8] E. Ernst, "Methodological aspects of traditional Chinese medicine (TCM)," *Annals of the Academy of Medicine Singapore*, vol. 35, no. 11, pp. 773–774, 2006.

[9] R. Q. Chen, C. M. Wong, and T. H. Lam, "Construction of a traditional Chinese medicine syndrome-specific outcome measure: the Kidney Deficiency Syndrome Questionnaire (KDSQ)," *BMC Complementary and Alternative Medicine*, vol. 12, article 73, 9 pages, 2012.

[10] T. X. Wu, H. C. Shang, Z. X. Bian et al., "Recommendations for reporting adverse drug reactions and adverse events of traditional Chinese medicine," *Chinese Journal of Evidence-Based Medicine*, vol. 10, no. 2, pp. 215–219, 2010.

[11] D. Tovey, *The Impact of Cochrane Reviews*, The Cochrane Library, 2010, http://www.thecochranelibrary.com/details/editorial/756937/The-Impact-of-Cochrane-Reviews.html.

[12] M. Clarke, "Standardising outcomes for clinical trials and systematic reviews," *Trials*, vol. 8, article 39, 2007.

[13] P. R. Williamson, D. G. Altman, J. M. Blazeby, M. Clark, and E. Gargon, "The COMET (core outcome measures in effectiveness trials) initiative," *Trials*, vol. 12, supplement 1, article A70, 2011.

[14] P. R. Williamson, D. G. Altman, J. M. Blazeby et al., "Developing core outcome sets for clinical trials: issues to consider," *Trials*, vol. 13, article 132, 2012.

[15] World Health Organization, *WHO Handbook for Reporting Results of Cancer Treatment*, WHO Publication, World Health Organization, Geneva, Switzerland, 1979.

[16] P. Tugwell and M. Boers, "OMERACT conference on outcome measures in rheumatoid clinical trials: introduction," *Journal of Rheumatology*, vol. 20, no. 3, pp. 528–530, 1993.

[17] P. Tugwell, M. Boers, P. Brooks, L. Simon, V. Strand, and L. Idzerda, "OMERACT: an international initiative to improve outcome measurement in rheumatology," *Trials*, vol. 8, article 38, 2007.

[18] R. H. Dworkin, D. C. Turk, J. T. Farrar et al., "Core outcome measures for chronic pain clinical trials: IMMPACT recommendations," *Pain*, vol. 113, no. 1-2, pp. 9–19, 2005.

[19] J. Schmitt and H. Williams, "Harmonising outcome measures for eczema (HOME). Report from the first international consensus meeting (HOME 1), 24 July 2010, Munich, Germany," *The British Journal of Dermatology*, vol. 163, no. 6, pp. 1166–1168, 2010.

[20] F. Gottrup, J. Apelqvist, and P. Price, "Outcomes in controlled and comparative studies on nonhealing wounds: recommendations to improve the quality of evidence in wound management," *Journal of Wound Care*, vol. 19, no. 6, pp. 239–268, 2010.

[21] I. P. Sinha, R. L. Smyth, and P. R. Williamson, "Using the Delphi technique to determine which outcomes to measure in clinical trials: recommendations for the future based on a systematic review of existing studies," *PLoS Medicine*, vol. 8, no. 1, Article ID e1000393, 2011.

[22] http://www.comet-initiative.org/.

[23] http://www.comet-initiative.org/about/whoweare.

[24] http://www.comet-initiative.org/about/overview.

[25] http://www.comet-initiative.org/meeting.

[26] S. L. Lai, "Key points about clinical effectiveness assessment of traditional Chinese medicine," *Journal of Guangzhou University of Traditional Chinese Medicine*, vol. 19, no. 4, pp. 245–250, 2002.

[27] J. J. Gagnier, H. Boon, P. Rochon, D. Moher, J. Barnes, and C. Bombardier, "Reporting randomized, controlled trials of herbal interventions: an elaborated CONSORT statement," *Annals of Internal Medicine*, vol. 144, no. 5, pp. 364–367, 2006.

[28] H. MacPherson, D. G. Altman, R. Hammerschlag et al., "Revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): extending the CONSORT statement," *PLOS Medicine*, vol. 7, no. 6, Article ID e1000261, 2010.