



## Research Paper

# The efficacy and safety of Dingji Fumai Decoction combined with metoprolol in premature ventricular contractions: a randomized controlled clinical trial

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### ABSTRACT

This study carried out a detailed analysis on the efficacy and safety of Data Flow Diagram (DFD) in the treatment of patients with Premature Ventricular Contractions (PVCs). The treatment group (50 patients) received 200 ml DFD every 8 h combined with 12.5 mg metoprolol every 12 h and the control group (50 other patients) received 12.5 mg metoprolol every 12 h alone for 4 weeks. At the baseline and endpoint, the clinical symptoms, signs, Holter, adverse events, laboratory examination and physical examination were determined in both groups and compared. The groups did not differ significantly in demographic and baseline clinical characteristics. The treatment group significantly decreased the TCM syndrome score ( $P = 0.005$ ) and the number of PVCs ( $P = 0.047$ ) compared with the control group. No adverse events occurred in this trial. The DFD seems to be safe and ameliorates the TCM syndrome score and the number of PVCs in patients with PVCs.

**Key words:** Traditional Chinese medicine, anti-arrhythmic, Dingji Fumai decoction, ventricular premature contraction, randomized controlled clinical trial.

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## INTRODUCTION

Cardiovascular disease is the world's leading cause of death, with 17.3 million deaths in 2008 and an estimated 23.6 million deaths by 2030 (Smith et al., 2012). In China, the death rate of cardiovascular disease accounts for more than 40%.

Cardiac arrhythmia is one of the most serious cardiovascular diseases. The harm of arrhythmia lies in that it not only aggravates the original heart disease such as accelerating the progression of heart failure, but also leads to sudden death, seriously threatening human health. The annual incidence clinically confirmed sudden cardiac death is about 0.36 to 1.28‰, and the actual incidence may be slightly higher, while ventricular arrhythmia is the main cause of sudden cardiac death (Marsman et al., 2014; Mendis et al., 2011). Clinically, ventricular arrhythmias are common with or without structural heart disease (Messineo, 1989). Modern medicine has developed from drug therapy to non-drug therapy, but both have certain limitations and adverse reactions (such as pro-arrhythmia), and some drugs can alleviate clinical symptoms

insignificantly.

TCM has been used in clinical practice for more than two thousand years (Chao et al., 2017) characterizing the entire view and syndrome differentiation, and has shown its unique advantages in the prevention, treatment, rehabilitation and health care of various diseases. TCM is a huge treasure house, and it has a long history of anti-arrhythmias. It is worth celebrating that great progress has been made in the research on the treatment of arrhythmias in recent years (Hao et al., 2015, 2017; Brenyo and Aktas, 2014).

DFD is an empirical prescription developed by Professor Luo, a national-level teacher tutor, according to the basic theory of TCM for the treatment of palpitation (equivalent to arrhythmia in modern medicine). It is composed of chuanxiong (*Chuanxiong Rhizoma*), Guizhi (*Cinnamomi Ramulus*), and Suanzaoren (*Ziziphi Spinosae Semen*), etc (Fu et al., 2019). DFD has a significant clinical effect in the treatment of Ventricular Premature Contraction (PVCs) and this randomized controlled clinical trial can provide

reliable clinical evidence.

## MATERIALS AND METHODS

### Drugs

DFD was made by the Chinese Pharmacy, Hospital (TCM) Affiliated to Southwest Medical University. The Metoprolol Tartrate tablets was purchased from the AstraZeneca Pharmaceutical Company.

### Protocol of the clinical trial

A randomized, positive controlled parallel-group trial was performed in the Hospital (TCM) Affiliated to Southwest Medical University (Luzhou, China). The trial was conducted from January, 1<sup>st</sup> to December, 31<sup>st</sup> 2018.

### Inclusion criteria

Chinese patients whose 12-lead electrocardiogram or dynamic electrocardiogram (Holter) shows they have PVCs applied to I ~ IV-A according to the American LOWN classification method in line with the TCM 'Heart blood asthenia of palpitation' syndrome diagnosis; cardiac ultrasonography shows left ventricular ejection fraction is more than 50% and discontinuation of any anti-arrhythmic drugs for 5 half-lives or more and / or Chinese medicine for 2 weeks or more before enrollment.

### Exclusion criteria

This include patients with high mental anxiety and depression (self-rating anxiety scale score above 70 or self-rating depression scale score above 73) and patients with mental illness; allergic to test ingredients or accessories; pregnant and lactating women and women planning pregnancy for nearly half a year; individuals who are participating in other clinical trials and finally minors.

The enrolled patients were randomized to the treatment (DFD combined with metoprolol) and control (metoprolol alone) group. Block randomization with computer generated random number table and sequentially numbered containers each representing a block consisting of ten patients was used for the treatment allocation. The patients were instructed to take 200 ml DFD every 8 h combined with 12.5 mg metoprolol every 12 h or 12.5 mg metoprolol every 12 h alone for 4 weeks. The patients were also asked to make no changes to their diet and physical activity compared to before trial. Further, the clinical symptoms, signs, Holter, adverse events, laboratory examination (routine of blood, urine and stool, liver and

renal function and electrolytes examination) determined by an autoanalyzer and physical examination were compared.

Primary outcome variables include the clinical symptoms, signs, number of PVCs events determined by the Holter, while the secondary outcome variables include adverse events, laboratory and physical examinations. Three different persons generated the random allocation sequence, enrolled the patients and assigned them to interventions. Patients adherence to the treatments was measured by counting returned bottles and asking how many doses of the drugs were (or were not) taken. Forty-four (44) patients in each group was the sample size calculated, considering type I error = 0.05, 90% power and the loss rate ≤ 10%.

IBM SPSS Statistics 24.0 software was used for statistical analysis. For all data, categorical variables were expressed as statistics, and continuous variables expressed as statistical mean and standard deviation (subject to normal distribution) or statistical median and quantile (not subject to normal distribution). The chi-squared test and independent sample t-test were used for data analysis and  $P < 0.050$  was considered statistically significant. The data were analyzed by the per protocol approach.

This study was approved by the Ethics Committee of Hospital (TCM) Affiliated to Southwest Medical University. The clinical trial was performed according to the revised Declaration of Helsinki, 2013. The participants gave written informed consent before enrolment. This trial was registered at Chinese Clinical Trial Registry (<http://www.chictr.org.cn>) as ChiCTR-INR-17013548.

## RESULTS

### Clinical characteristics of patients

According to the inclusion and exclusion criteria, this trial enrolled 100 patients (50 patients in each group), which lost 8 patients (5 patients in the treatment group and 3 patients in the control group) and suspended 0 patient; finally, 92 patients (45 patients in the treatment group and 47 patients in the control group) completed the trial. **Table 1** shows that the groups did not differ significantly in demographic and baseline clinical characteristics.

### The comparison of efficacy

#### *The comparison of total effective rate*

The treatment group significantly decreased the TCM syndrome score ( $P = 0.005$ ) and the number of PVCs ( $P = 0.047$ ) compared with the control group (**Table 2**).

#### *The stratification comparison of total effective rate*

Further analysis was carried out according to gender, age

**Table 1:** Demographic and baseline clinical characteristics.

Term	T	C	P value	
N	45	47	-	
Gender (male / female)	18/27	24/23	0.29	
Age (years old)	73(65.5-80)	75(68-80)	0.67	
Basic heart diseases	CHD	2	0	
	HHD	19	24	
	PHD	13	15	
	DCM	6	3	0.46
	VHD	0	1	
	Others	4	4	
	None	1	0	
Holter	Single PVCs	1276(786-4176.5)	1565(817-4613)	0.87
	VT	0(0-1)	0(0-0)	0.27
	Single APC	245(4.5-2530.5)	75(0-833)	0.18
	AT	1(0-33)	0(0-7)	0.11
	Double PVCs	0(0-9.5)	1(0-4)	0.92
	Triple PVCs	0(0-3)	0(0-3)	0.67
	Paired PVCs	3(0-36)	3(0-18)	0.32
TCM syndrome score	16.47±4.80	17.81±5.64	0.22	

The independent sample t-test was used for data analysis.  $P < 0.05$  is statistically significant. **T:** Treatment group, **C:** Control group, **CHD:** Coronary heart disease, **HHD:** Hypertensive heart disease, **PHD:** Pulmonary heart disease, **DCM:** Dilated cardiomyopathy, **VHD:** Valvular heart disease, **PVCs:** Ventricular premature contractions, **VT:** Ventricular tachycardia, **APC:** Atrial premature contraction, **AT:** Atrial tachycardia, **TCM:** Traditional Chinese medicine.

**Table 2:** The comparison of total effective rate.

Term	Group	Total effective	Invalid	$\chi^2$	P value
TCM syndrome score	T	44	1	7.93	0.005
	C	37	10		
PVCs	T	37	8	3.93	0.047
	C	30	17		

The Pearson chi-squared test was used for data analysis.  $P < 0.05$  is statistically significant. **TCM:** Traditional Chinese medicine, **PVCs:** Ventricular premature contractions, **T:** Treatment group, **C:** Control group.

and basic heart diseases. From the analysis it was observed that the total effective rate of all stratifications in the treatment group was better than that in the control group. Moreover, only the efficacy evaluation of TCM syndromes in female of gender stratification and  $\geq 75$  years old of age stratification, and the efficacy evaluation of PVCs in pulmonary heart disease of basic heart diseases

stratification showed statistically significant differences ( $P = 0.030, 0.008$  and  $0.043$ , respectively) (Table 3).

### ***The comparison of safety***

The patients did not report any adverse drug effect.

**Table 3:** The stratification comparison of total effective rate.

Variable	Term	Group	Total effective	Invalid	X <sup>2</sup>	P value <sup>a</sup>
Gender (male / female)	TCM syndrome score	T	18/26	0/1	-/-	0.095 / 0.030
		C	20/17	4/6		
	PVCs	T	16/21	2/6	-/2.579	0.151 / 0.108 <sup>b</sup>
		C	17/13	7/10		
Age (≥ 75 / < 75 years old)	TCM syndrome score	T	22/22	0/1	-/-	0.008 / 0.287
		C	18/19	7/3		
	PVCs	T	19/18	3/5	3.078/1.171	0.079 <sup>b</sup> / 0.279 <sup>b</sup>
		C	16/14	9/8		
Basic heart diseases (CHD / PHD)	TCM syndrome score	T	18/13	1/0	-/-	0.090 / 0.139
		C	18/12	6/3		
	PVCs	T	15/11	4/2	-/-	0.403 / 0.043
		C	17/7	7/8		

The <sup>a</sup> Fisher's exact test and <sup>b</sup> Pearson chi-squared test were used for data analysis.  $P < 0.05$  is statistically significant. **CHD:** Coronary heart disease, **PHD:** Pulmonary heart disease, **TCM:** Traditional Chinese medicine, **PVCs:** Ventricular premature contraction, **T:** Treatment group, **C:** Control group.

Laboratory indicators showed no significant changes from baseline to 4 weeks after treatment. Physical examination also did not find any abnormalities.

## DISCUSSION

The clinical manifestations of ventricular arrhythmias vary widely; patients can be asymptomatic, hemodynamically unstable, and there might also be occurrence of sudden cardiac death. PVCs is common, whether or not combined with structural heart disease and the rate is about 1 to 4% in the general population, respectively. Studies have shown that the prevalence detected by 12-lead electrocardiogram is only 1%, while the detection rate by 24 h or 48 h dynamic electrocardiogram is as high as 70% (Ng, 2006). Moreover, the incidence of PVCs prevalence increases gradually with age, which is less than 1% in children under 11 and as high as 70% in the elderly over 75% (Camm et al., 1980).

With regard to the treatment of PVCs, modern medicine has developed from drug therapy to non-drug therapy. Non-drug therapy, as an instrumental adjuvant therapy, is an important supplement to drug therapy. Catheter ablation can eradicate 70 to 100% of patients with PVCs (Pedersen et al., 2014). However, in recent years, reports of complications of non-drug therapy are not uncommon (Wang et al., 2018). Implantable cardioverter defibrillators are prone to cause psychological maladaptation and anxiety, etc (Prudente, 2005).

Moreover, non-drug therapy is relatively expensive, which has limited its clinical use and promotion, and it is difficult for many patients to benefit from it.

However, drug therapy is still the cornerstone of anti-

arrhythmia therapy and plays an irreplaceable role. It is often used as the preferred treatment and long-term maintenance treatment (Al-khatib et al., 2018). Besides, there are certain limitations and adverse reactions in both drug therapy and non-drug therapy. All anti-arrhythmic drugs have varying degrees of arrhythmogenic effects, including arrhythmias that are not present before administration and exacerbating the original arrhythmia, with the highest incidence of arrest and conduction block. The incidence of arrhythmia caused by different types of anti-arrhythmic drugs is about 5.9 to 37%, respectively.

TCM is a huge treasure house with a long history of anti-arrhythmia therapy. In recent years, research on the treatment of arrhythmia with TCM has made great progress (Hao et al., 2017; Liang et al., 2019) and has been well received at home and abroad. Wenxin Keli (Wei et al., 2015), Shensong Yangxin capsule (Liu et al., 2018), Shenxian-shengmai oral liquid (Liu et al., 2018) and other anti-arrhythmic drugs have confirmed the efficacy by clinical research. DFD mainly uses methods of enriching blood, nourishing heart, tranquilization and nourishing Yin (Fu et al., 2019).

From the results attained it is evident that proper attention should be paid to the advantages of TCM, gradually improve the diagnosis and treatment plan, combine Chinese and Western medicine, learn from each other's strengths, and improve efficacy. In this trial, we found out that DFD combined with metoprolol can significantly ameliorates the TCM syndrome score and the number of PVCs in the patients with PVCs than metoprolol alone. Moreover, there was no adverse drug effect. Our previous animal experiments also showed that DFD has no obvious side effects (Fu et al., 2019). Finally, long-term

clinical trials investigating the efficacy of DFD in the treatment of PVCs seem warranted.

## Conclusions

From the results of the analysis conducted the DFD seems to be safe and ameliorates the TCM syndrome score and the number of PVCs in the patients with PVCs.

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