The Utility of Traditional Chinese Medicine (Shenmai) in the Cardiac Rehabilitation after Coronary Artery Bypass Grafting: a Single-Center Randomized Clinical Trial

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Introduction

Shenmai, a traditional Chinese medicine has been shown to improve cardiac function during coronary artery bypass grafting, has not yet been assessed as adjunctive treatment to be used during cardiac rehabilitation. Shenmai is a form of medication which is administered orally or intravenously. It is widely used in clinics for improving heart functions by regulating blood pressure, dilating coronary arteries, and generating antioxidative effect.[1,2] Studies have demonstrated that Shenmai has a positive inotropic effect and improves exercise tolerance among patients suffering from coronary artery disease and heart failure.[3,4]

Cardiac rehabilitation after coronary artery bypass grafting is highly recommended by the clinical practice guidelines.[5] In China, however, cardiac rehabilitation is only 24% available, and only in the large medical centers, and the percentage of patients undergoing cardiac rehabilitation is relatively low.[6] Due to cultural beliefs, Chinese patients are more willing to accept traditional ways of rehabilitation. For example, they are more likely to perform Taiji as a way of exercise instead of walking on a treadmill or riding an exercise bike. They also prefer traditional Chinese herbs and medicine since they are thought to be more natural, cheaper and safer.

Shenmai is extracted from several Chinese herbs, mainly from Panaxginseng and Ophiopogon japonicus. It is approved by the China Food and Drug Administration since 1995.[7] The formula of the compound is standardized, and mass produced in two forms, capsule or injection. Considering its multi-effect on the cardiovascular system,[8] Shenmai is assumed as a complement to contemporary cardiac rehabilitation after coronary artery bypass grafting. However, the effect of Shenmai as a complement to standard cardiac rehabilitation in patients who received coronary artery bypass grafting is unknown. Therefore, the aim of this study is to examine the efficacy of Shenmai as a complement to standard cardiac rehabilitation in Chinese

patients undergoing coronary artery bypass grafting, mainly in the patients with mild to moderate impaired heart function (New York Heart Association (NYHA) classification Ⅱ-Ⅲ).[7,9]

Methods

The study was conducted by Beijing Anzhen Hospital, Capital Medical University, Beijing, China. It was approved by the independent Medical Ethics Committee of Anzhen Hospital before the start (No. 2016P02). The clinical trial has been registered at Chinese Clinical Trial Registry with the name 'The utility of Chinese traditional medicine (Shenmai) in the cardiac rehabilitation after coronary artery bypass graft: a randomized controlled trial' and the registration number is ChiCTR1800015547. The data collection began in March 2018 and ended in May 2018.

The study was a single-center randomized clinical trial. A total of 166 eligible patients received coronary artery bypass grafting were enrolled and allocated equally to the Shenmai and control group (83:83). The randomization was conducted based on random numbers generated by a random number generator from the clinical trial data management center of Anzhen Hospital and a random allocation occurred just after the recruitment. All participants received standard cardiac rehabilitation according to the clinical guidelines, while participants in the Shenmai group was treated with Shenmai (injection and capsule sequential) additionally. A 30-day follow-up was completed through the outpatient's department. Participants were assessed at baseline, on the day of discharge and 30-day follow up.

Setting and participants

From March 2018 to April 2018, a total of 166 patients received coronary artery bypass grafting in our center were consecutively enrolled according to the inclusive criteria. Individuals were eligible if they were 1) ≥18 years old; 2) diagnosed as coronary artery disease and planned

to receive the coronary artery bypass grafting, no matter what other procedure was added simultaneously; 3) gave informed consent; 4) competent to complete the 6-minute walking test without any assistance. The patients were excluded when: 1) with severe comorbidity that can't finish the 6-minute walking test alone, such as heart failure, stroke with severe sequela, multi-organ dysfunction or disable; 2) with tumor that the predicted life time is less than 3 months.

Intervention

Participants in both groups received standard cardiac rehabilitation after coronary artery bypass grafting. In addition, the Shenmai group received Shenmai injections and capsules, while the control group received no additional treatment.

The rehabilitation program was designed according to the clinical guidelines,[10] including exercise training, focusing on aerobic exercise such as a combination of walking or jogging on a treadmill or stationary surface, stair climbing, and step aerobics. It began right after the patients could get out of bed. The intensity of the training program was established according to participants' clinical condition and tolerance for symptom-limited exercise. Exercise training was conducted twice a day and was supervised by members of the cardiac rehabilitation staff. Each exercise session lasted up to 60 minutes (as tolerated) and included at least 5 minutes each for warm-up and cool-down exercises.[11]

Shenmai is mainly extracted from two plants, Panaxginseng and Ophiopogon japonicus.[12] It has been mass-produced as a patented drug based on the national standards approved by CFDA (China Food and Drug Administration). Shenmai injection used in our research was manufactured in accordance with applicable GMP by Qing Chunbao Pharmaceutical Co., Ltd (Hangzhou, China). It was administrated during the inpatient period (100ml/day). Shenmai

capsule was manufactured by Xinbang Pharmaceutical Co., Ltd (Guizhou, China) and was prescribed after the day discharged from our hospital and back to home (3.6g/day).

Measurements

These baseline clinical outcomes data were collected based on medical record, which include age, gender, body mass index (BMI), smoking history, family history of coronary artery disease, et al.

The 6-minute walking test was implemented at three time points. The first point was on the day just before the operation. The second point was on the day when participants were discharged from the hospital and sent home. The third point was on the last day of 30-day, post-discharge follow-up. The first and second measurements were conducted in-hospital. For the third (follow-up) test, all participants were required to return to the outpatient clinic to perform the walking test.

The 6-minute walking test was conducted by two special assistant investigators. They instructed the participants to implement the test and measured the distance. They were supervised by research team members during the entire measurement to ensure their blindness to the allocation.

The patients were instructed to walk as far as possible along a 20-m straight, flat hospital corridor in 6 minutes. Patients who showed any uncomfortable symptoms (e.g. angina, severe dyspnea, dizziness and musculoskeletal pain) were told to stop or slow their walking and to restart if symptoms disappeared within 6 minutes. The participants were not encouraged to go beyond their tolerance by researchers. The total distance walked was measured to the nearest meter of integer and recorded.

Clinical outcomes.

The primary outcome was the distance of 6-minute walking test on the point of discharge;

The secondary outcomes related to the safety and efficiency of the intervention, such as perioperative and follow-up mortality, MI, stroke, reoperation, the length of stay in ICU, the duration under the mechanical ventilation and the length of stay after the operation in hospital. The distance of 6-minute walking test at the point of 30-day follow up was also a secondary endpoint in this study.

Sample size calculation

The sample size was estimated based on the expected improvement in the distance of 6-minute walking test on the day of discharge through the previous clinic trial that applied Shenmai in the patients with heart failure.[3] It was expected that a 32 meters improvement in Shenmai group and the standard deviation (SD) of 65 meters was derived from previous study. Given a power (1-β) of 80% and $\alpha = 0.05$ (two-side), 66 patients would be required for each group to detect the superiority. Moreover, considering the dropout rate was approximately 20%, a total of 166 patients (83 per treatment group) was needed to be randomized to achieve the required number of patients for the efficacy analysis.

Statistical analysis

Statistical analyses were performed using the R statistical package (R version 3.4.2 (2017-09-28)). The continuous variables were calculated for mean and standard deviations. Comparison of normal distributed data from the patients who completed both initial and follow-up exercise test was performed using the Student's t-test between two groups. The non-normally distributed data was analyzed using the Wilcoxon rank sum test. Categorical variables were presented as counts and percentages. The differences in categorical variables between patient subgroups were evaluated with chi-square test or Fisher exact test as appropriate.

Linear mixed model was performed with SAS version 9.4 (SAS Institute, Cary, NC) to examine the differences of 6-min walking distance between two groups over time. A two-tailed p value < 0.05 was considered statistically significant. Intension to treat principle was performed, that is, we still included participants for data analysis if they withdrew study.

Results

This trial was implemented according to the flow diagram (Figure 1). From March 2018 to April 2018, a total of 213 patients were approached, but only 166 were recruited and allocated randomly into two equal groups. All participants completed the clinical data collection along with the basal 6-minute walking test. The participants of Shenmai group were administrated the Shenmai injection right after the surgery for 9.28 ± 3.75 days and then changed to the Shenmai capsule for 30 days. Only two suffered from severe surgical complications, the other 164 patients accomplished the 6-minute walking test on discharge and 30-day follow up. No participants dropped out during the follow up.

The demographic characteristic of the study cohort was shown in Table 1. The sample (n=166) was predominately male (84%). The mean age was 61.12 ± 9.13 years. The baseline characteristics between two groups were roughly equal. The procedural characteristics were also comparable (Table 2).

The post-operative outcomes of the study were shown in Table 3. There was one death in the control group, owing to the postoperative myocardial infarction (MI) and acute heart failure. It happened the day after the operation and appeared as progressive hypotension. The electrocardiogram and myocardial enzyme helped make the final diagnosis (the cardiac troponin I was greater than the upper bound (85ng/l) of the test kit). An intensive therapy was administered shortly after, including the intra-aortic balloon pump (IABP), but failed. A patient

in the Shenmai group suffered severe stroke and couldn't extubate in the ICU. After prolonged hours of mechanical ventilation and length of stay in the ICU, this patient was transferred to the department of Neurology to receive rehabilitation. There was no other death, stroke, MI and reoperation during the in-hospital stage. The duration of the length of stay in ICU of the entire cohort was 62.64 ± 58.40 [95% CI: 53.69, 71.59] hours. The hours of mechanical ventilation were 16.07 ± 32.54 [95% CI: 11.06, 21.09]. There was no death, stroke, MI, reoperation, or rehospitalization in the period of follow up.

The 6-minute walking test was implemented according to the protocol. The baseline distance of the two groups before the operation was comparable. As shown in the linear mix model analysis, there were group ($p = .005$) and time points of measurement ($p < .001$) effects on the 6-min walking distance. However, there was no interaction effect between group and time points of measurement. Participants in the Shenmai group walked longer distance in meters compared with the control group on the day of discharge (314.54 ± 64.14 vs. 271.29 ± 76.82, $P < 0.001$), while there were no significant differences before operation (399.72± 93.19 vs. 403.67 ± 91.99, $p = .78$) or on the 30-day follow-up (436.54 ± 67.64 vs. 421.64 ± 83.53, $p = .21$). Also, there was greater improvement at the point of 30-day follow-up compared to the point of pre-operation and discharge in both groups ($p_s < .001$) (table 4). These differences were maintained after adjusting for age, gender, BMI, smoking history and post-operation length of stay in hospital. The post-operation length of stay in hospital was slightly longer in Shenmai group than control group (9.28 ± 3.75 days vs. 8.60 ± 2.50 days) and might have influence on the exercise tolerance comparison at discharge; however, the conclusion did not change after adjusting this confounder.

Discussion

As shown in this study, Shenmai significantly improved the exercise tolerance at the end of the in-hospital stage of cardiac rehabilitation. At the 30-day follow-up, the Shenmai group reached a greater distance in the 6-minute walking test compared with the control group, but there was no statistically significant difference. Other outcomes were comparable between the two groups and no side effects were experienced by the Shenmai group.

Shenmai is widely used in China as a complementary treatment for either acute or chronic heart failure. It is extracted from Panax ginseng and Ophiopogon japonicus and usually mass-produced as a patented drug in different forms (including capsule, powder, oral liquid and injection) based on a standardized formula. In clinical practice, Shenmai is used to ease the symptoms and discontinued after the relief of symptoms or in the case of disease remission. Adverse effects are rare and mild; an allergic reaction is most common.[13]

In this study, we administrated Shenmai in the cardiac rehabilitation after coronary artery bypass grafting. An exercise improvement was achieved in the early postoperative stage. Although the key ingredient in Shenmai is complex and not very clear, the study indicated the potential mechanism in five aspects, including positive inotropic effect,[1] dual-directional regulation on blood pressure,[14] improving hemodynamic parameters,[15] delaying the cardiac remodeling,[2] and antioxidative effect.[16] The cure effect is also shown in many other aspects, such as reduction of the mortality, improvement of function classification according to the New York Heart Association (NYHA), and decrease of the adverse effects.[13]

Similar to other traditional Chinese medicines, Shenmai is too obscure to be understood based on traditional Chinese medicine theory. Then inevitably, we will ask why a significant difference in the 6-minute walking test was not demonstrated on the 30-day follow-up between two groups? Does it mean that Shenmai has no effect on the cardiac rehabilitation at all, even

though the significant improvement was shown at discharge? When looking insight into this study, two major facts should be paid attention. Considering the study design, the point of discharge is the primary endpoint, the 30 days outcome is secondary endpoint. Perhaps the efficacy of study design is insufficient for a positive outcome at 30-day follow up, because the sample size calculation is based on information at the time point of discharge. Further study will focus on the long-term follow up based on the data demonstrated by this trial. The second possible reason was the change of Shenmai from injections to capsules when discharged. The capsule of Shenmai needs much more time and dosage to show its cure effect. The third possible reason is that we did not provide placebo to the control group, which might confound results.

Chinese herbs and medicine closely relate to the cultural belief that traditional Chinese medicine is more natural, effective, cheap and has fewer adverse effects. In the traditional Chinese medicine theory, when treating the patient as an entirety, the 'Qi' deficiency is the critical factor during the cardiac rehabilitation. Many methods from traditional Chinese medicine have been used in the exercise prescription of cardiac rehabilitation to improve the deficiency, such as Taiji and Ba Duanjin. Given this study and others, Shenmai also showed significant benefit in improving the exercise tolerance.[3] Many other treatment ways originated from the traditional Chinese medicine have similar efficacy. Future study needs examine long-term effect and the effective ingredients in Shenmai, which need to be purified and fixed.

Clinical messages

- Shenmai improves the exercise tolerance in the early stage of the cardiac rehabilitation according to this study. It is safe and effective when administrated to patients who received coronary artery bypass grafting.

- The traditional Chinese medicine can be complementary to the standard cardiac rehabilitation.

Competing interests, and source of funding

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Contributors

CX Z initiated the study; CX Z, YG Z and TC design the study; CX Z, YG Z wrote the paper; YG Z and TC decided on the analytic strategy; SY W monitored progress; M X is the supervisor and consultant of this study; CX Z is the Principal investigator.

Table.1. Clinical demographics characteristics of patients

	Control (n=83)	Shenmai (n=83)	P value
Sex (male %)*	69 (83)	70 (84)	0.83
Age (year)#	61.69 ± 8.60	60.55 ± 9.65	0.42
BMI (kg/m^2)#	25.30 ± 3.24	25.71 ± 3.01	0.39
Smoking history (%)*	45 (54)	47 (57)	0.75
Family history of CAD (%)ǂ*	6 (7)	4 (5)	0.75
Pre-MI (%)*	52 (63)	38 (46)	0.029
DM (%)*	23 (28)	26 (31)	0.61
Hyperlipoidemia (%)*	49 (59)	49 (59)	1.00
Hypertension (%)*	55 (66)	50 (60)	0.42
Stroke (%)*	7 (8)	7 (8)	1.00
Renal disfunction (%)ǂ*	2 (2)	1 (1)	1.00
PVD (%)ǂ*	0 (0)	1 (1)	1.00
NYHA			
Ⅰ (%)ǂ*	3 (4)	1 (1)	0.62
Ⅱ (%)*	53 (64)	62 (75)	0.13
Ⅲ (%)*	26 (31)	19 (23)	0.22
Ⅳ (%)ǂ*	1 (1)	1 (1)	1.00
LVEF (%)ł*	57.69 ± 8.79	58.53 ± 9.77	0.44
LM disease (%)*	35 (42)	30 (36)	0.22
Creatinine (umol/L)ł#	89.17 ± 22.87	87.72 ± 19.18	0.67
TC (mmol/L)#	4.34 ± 1.00	4.12 ± 1.15	0.66
ALB (g/L)ł#	39.66 ± 4.35	40.60 ± 3.94	0.09
hs-CRP (ug/L)ł#	3.08 ± 3.84	2.1 ± 2.22	0.20

BMI: body mass index; MI: myocardial infarction; DM: Diabetes mellitus; PVD: peripheral vascular disease; NYHA: New York Heart Association Functional Classification; LVEF: left ventricular ejection fraction; LM: left main coronary artery; TC: total cholesterol; ALB: serum albumin; hs-CRP: high-sensitivity C-reactive protein;

ǂ: Fisher's exact test; ł: Wilcoxon rank sum test

*: number of patients (percentage)

#: mean ± standard deviation (SD)

Table.2. Characteristics of intraoperation

	Control (n=83)	Shenmai (n=83)	P value
On pump CABG (%)*	41 (49)	42 (51)	0.88
CPB time (mins)Ŧ#	117.10 ± 31.69	112.79 ± 28.50	0.60
Clamp occlusion time#	78.34 ± 25.03	73.5 ± 24.51	0.38
Simultaneous heart valve surgery (%)*	7 (8)	7 (8)	1.00
LIMA in use (%)*	62 (75)	68 (82)	0.26
No. of SVG grafts			
SVG grafts = 1 (%)*	12 (14)	18 (22)	0.23
SVG grafts = 2 (%)*	29 (35)	37 (45)	0.20
SVG grafts = 3 (%)*	33 (40)	23 (28)	0.10
SVG grafts = 4 (%)ŧ*	8 (10)	2 (2)	0.10

CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; LIMA: left internal mammary artery; SVG: saphenous vein graft;

Ŧ: Wilcoxon rank sum test; ŧ: Fisher's exact test

*: number of patients (percentage)

#: mean ± standard deviation (SD)

Table.3. Differences in Postoperative Outcomes Between Groups

	Control (n=83)	Shenmai (n=83)	P value
Mortality (%)Ⱡ*	1 (1)	0	1.00
Stroke (%)Ⱡ*	0	1 (1)	1.00
ICU LOS (hours)ɬ#	59.01 ± 38.67	66.28 ± 73.09	0.82
Mechanical ventilation (hours)ɬ#	13.90 ± 9.88	18.24 ± 44.99	0.63
Postoperative LOS in hospital (day)ɬ#	8.60 ± 2.50	9.28 ± 3.75	0.43

ICU: intensive care unit; LOS: length of stay;

Ⱡ: Fisher's exact test; ɬ: Wilcoxon rank sum test

*: number of patients (percentage)

#: mean ± standard deviation (SD)

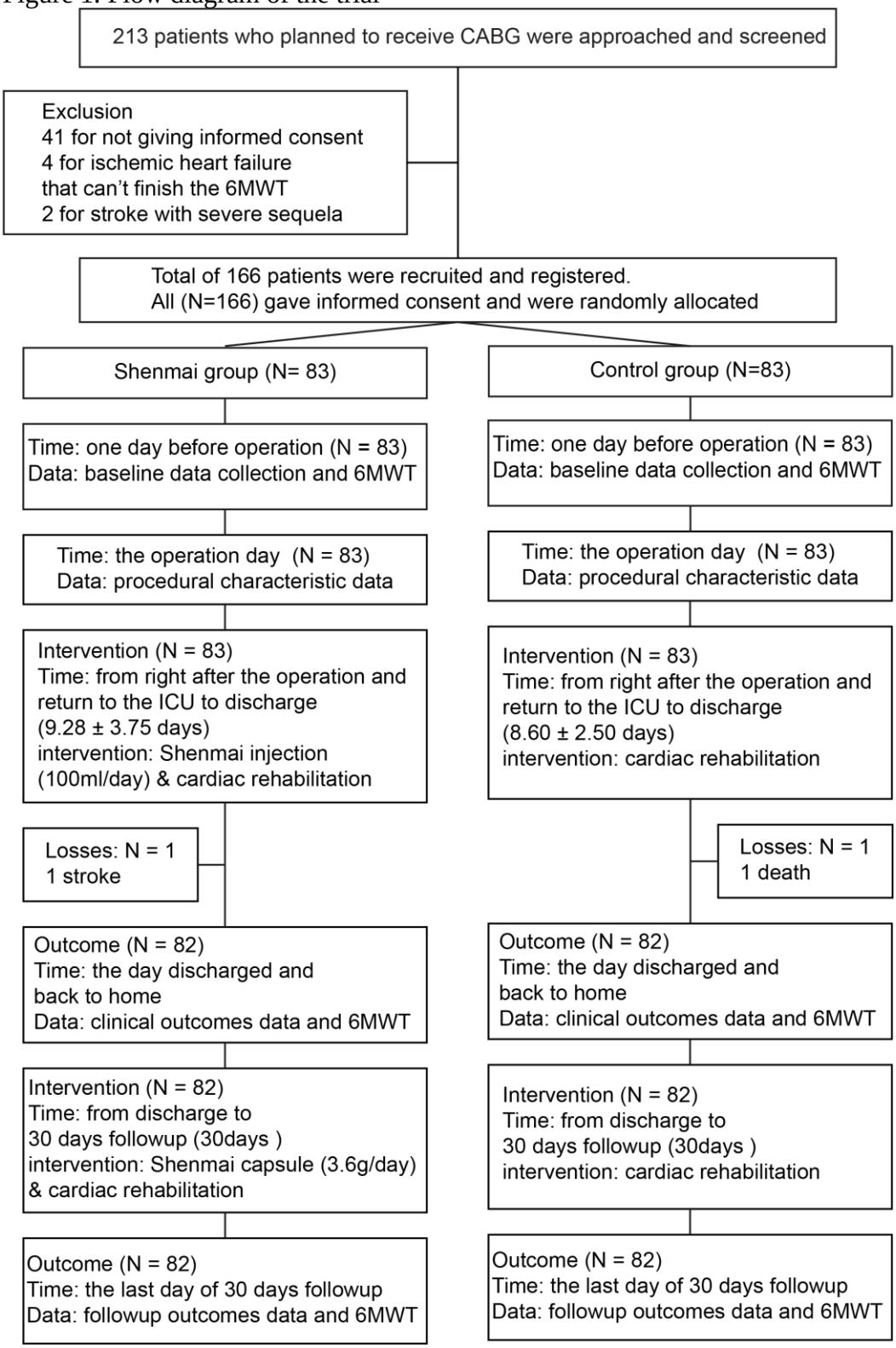
Table.4. Differences in Six-Minute Walking Test Between Groups over Time

	Control (n=83)	Shenmai (n=83)	P-values		
			group x time	group	time
6MWT distance before surgery (meters) #	399.72 ± 93.19	403.67 ± 91.99	0.07	0.005	<0.001
6MWT distance at discharge (meters) #	271.29 ± 76.82	314.54 ± 64.14			
6MWT distance at 30-day follow up (meters) #	421.64 ± 83.53	436.54 ± 67.64			

6MWT: six-minute walking test; P-values for between group differences before surgery, at discharge and 30-day follow-up was 0.78, <.001 and 0.21, respectively. These differences were maintained after adjusting for age, gender, BMI, smoking history and post-operation length of stay in hospital.

#: mean ± standard deviation (SD)

Figure 1. Flow diagram of the trial



CABG: coronary artery bypass grafting; MI: myocardial infarction; ICU: intensive care unit; 6MWT: 6-minute walking test;

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