Effects of Shenmai injection on the values of CO, SV, and EF in patients undergoing off-pump coronary artery bypass graft
A randomized, clinical trial
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Abstract
Background: To explore the effects of Shenmai (SM) injection on the values of cardiac output (CO), stroke volume (SV), and the ejection fraction (EF) in patients treated with off-pump coronary artery bypass graft (OPCABG).

Methods: Forty patients undergoing OPCABG were randomly divided into SM group (n=20) and the 5% glucose (G) group (n=20). The control liquids were injected from the beginning of the operation to the start of coronary artery bypass graft (CABG). The values of CO, SV, and EF before induction (t1), at the beginning of operation (t2), 30 minutes after the start of operation (t3), at the beginning of coronary artery bypass graft (t4), at the end of coronary artery bypass graft (CABG) (t5), and at the end of operation (t6) were recorded.

Results: The values of CO, SV, and EF in the patients of SM group at t3 to t6 were found to be significantly higher than those at t1 (P < .05). The values of CO, SV, and EF in the patients of G group were found to be increased at t5 and t6 (P < .05). At t3 and t4, the values of CO, SV, and EF in SM group were significantly higher than those in the G group (P < .05).

Conclusion: In patients with OPCABG, the infusion of SM injection can effectively increase the values of CO, SV, and EF and increase the safety of anesthesia management.

Keywords: cardiac output, ejection fraction, off-pump coronary artery bypass graft, Shenmai injection, stroke volume

1. Introduction
Coronary artery bypass grafting (CABG) is the preferred treatment method of coronary artery disease.1] Off-pump coronary artery bypass graft (OPCABG) can avoid the physiological disturbance with few complications, quick recover, and low cost.2]–3] The study on OPCABG has become a hot spot for surgical treatment of coronary heart disease.4]–5] With the development of rapid postoperative rehabilitation, the great challenge for anesthesiologists and surgeons is to improve heart functions and prevent myocardial ischemia and hypoxia. According to the Traditional Chinese Medicine theory, Shenmai (SM) injection has the function of invigorating qi, nourishing yin and replenishing bodily fluids.6]–10] Shen and Mai are the Chinese abbreviations of red ginseng and ophiopogon japonicas, and a large number of ginseng total saponins are contained in red ginseng. SM injection which contains 2 herbs, namely ginseng and ophiopogon japonicas, is developed and manufactured by Hangzhou Chiatai Qingchunbao Pharmaceutical Co, LTD in China.11 It is widely used to clinical and the toxicity of SM injection has been evaluated, which is generally considered to be safe to use.11,12] A study reports that SM has the effects of improving heart functions, balancing blood pressure, dilating the coronary arteries, increasing blood supply, reducing oxygen consumption, eliminating surplus free radicals, and so on.13] The purpose of this study is to explore the effects of SM injection on the values of cardiac output (CO), stroke volume (SV), and the ejection fraction (EF) in patients treated with OPCABG as well as the safety of anesthesia application. In this study, we concluded that the infusion of SM injection can effectively increase the values of EF, SV, and CO in patients treated with OPCABG and increase the safety of anesthesia management.

2. Materials and methods
2.1. Materials
A total of 40 patients (age, 46–74 years) scheduled for surgery under general anesthesia were enrolled in this study. Patients with
an American Society Anesthesiologists physical status of III or IV, those with a history of adverse effects caused by the study drugs, and those with severe respiratory failure, severe left ventricle dysfunction (EF < 35\%), severe uncontrolled hypertension (HTN) or hypotension, pacemaker or intracardiac devices, and bradycardia or arrhythmia were excluded. Patients with bleeding >1000mL during or after surgery, patients with >4 grafts were also excluded. This study was approved by the Medical Ethics Committee of Linyi City People’s Hospital (NO: KY2013004), Linyi, China.

2.2. Methods

After obtaining informed consent from all the patients, we randomized them into 2 groups. The SM group was given 60 mL of SM injection which was diluted to 150 mL with 5% glucose (G) solution when the skin was cut at the speed of 150 mL/hour, while the G group was given 150 mL of 5% G at the same speed and the same time as the SM group. Patients of 2 groups were continuously given dopamine and nitroglycerin. After successful arterial puncture under local anesthesia, the Vigileo monitor was connected to the patients via a FloTrac pressure sensor, and the data were collected continuously after calibration.

General anesthesia was induced and maintained by the same method. After establishing full cardiovascular monitoring, general anesthesia was induced with sufentanil 1 \( \mu \)g/kg, midazolam 0.05 mg/kg, lidocaine, and etomidate 1 to 2 mg/kg until loss of eyelid reflex. Orotracheal intubation was facilitated with 0.1 mg/kg cisatracurium. Routine airway and ventilator management were used as appropriate for the type of surgery. Anesthesia was maintained with continuous infusion of remifentanil 0.2 \( \mu \)g/kg/hour, propofol 4 mg/kg/hour, and sevoflurane 1% to 2% until patient transfers to open heart ICU. After the mechanical ventilation, transesophageal echocardiography was used to guide the puncture of right internal jugular vein. BIS monitoring and nasopharyngeal temperature and urine monitoring were given. A total of 5 \( \mu \)g/kg/min of dopamine, 0.6 \( \mu \)g/kg min of nitroglycerin, and 0.1 \( \mu \)g/kg min of phenylephrine were chosen as vasoactive drug.

2.3. Monitoring indicators

The values of CO, SV, and EF of the 2 groups were recorded before the induction of anesthesia (t1), at the start of surgery (t2), 30 minutes after the start of surgery (t3), at the beginning of coronary artery bypass graft (t4), at the end of coronary artery bypass graft (t5), and at the end of surgery (t6).

2.4. Statistical analysis

All the statistical analyses were using the SPSS (version 20, IBM logo,ibm.com). All data are presented as mean ± standard deviation. Demographic data were analyzed by Student t test or Mann–Whitney U test. Analysis of variance for repeated measures was used to analyze hemodynamic changes and CO, SV, EF, over time between 2 groups.

3. Results

3.1. Compared to G injection, SM injection was more effective on the values of CO, SV, and EF

We firstly compared the general information of the 2 groups before surgery, resulting that general information of the 2 groups showed no significant differences (Table 1). The variables of coronary artery disease and EF in patients of the study were not significantly different in 2 groups of study (\( P > .05 \)) (Table 2). All the patients were treated with the same group of cardiac surgeons, and the surgical methods were all the same. Effects of hemodynamics and CO, SV, EF in the SM group were detected, and the results showed that the values of CO, SV, and EF in the SM group at t5 to t6 were found to be significantly higher than those at t1 (\( P < .05 \)) (Table 3 and Fig. 1). Equally, effects of hemodynamics and CO, SV, EF in the G group were detected, and the results showed that the values of CO, SV, and EF in the G group were found to be increased at t3 and t5 (\( P < .05 \)) (Table 3 and Fig. 1). However, the values of CO, SV, and EF in the SM group were significantly higher than those in the G group (\( P < .05 \)) at t3 and t4 (Table 3 and Fig. 1), indicating that compared to G injection, SM injection was more effective on the values of CO, SV, and EF.

4. Discussion

SM injection stemmed from ancient traditional Chinese prescription of shenmaisan. It contains ginseng saponin, ginseng polysaccharides, ophiopogonin, organic acids, and so on.\(^{[6]}\) The studies have confirmed that it can promote coronary blood flow, reduce myocardial oxygen consumption,\(^{[11,12]}\) inhibit apoptosis of myocardial hypoxia and provide myocardial protection,\(^{[11–13]}\) reduce stress, improve antioxidant capacity, regulate, and promote immune functions.\(^{[14,15]}\) Cardiac effect of SM injection is stable and long-lasting, which is consistent with the perioperative medication characteristics of coronary artery bypass surgery. Tian et al.\(^{[16]}\) has confirmed that SM injection given 1 week before surgery and 1 week after CABG can improve cardiac functions and protect the heart.

### Table 1

| Comparison of general information. | SM (n = 20) | G (n = 20) | P |
|---|---|---|---|
| Age (y) | 65 ± 9 | 67 ± 7 | .525 |
| Sex (male\%) | 11 (55) | 12 (60) | .749 |
| Weight (kg) | 62.05 ± 11.42 | 63.96 ± 8.49 | .552 |
| Height (cm) | 168.45 ± 5.81 | 166.14 ± 6.02 | .224 |
| Hypertension (Yes/No) | 16/4 | 15/5 | 1.000 |
| Diabetes (Yes/No) | 8/12 | 6/14 | .507 |
| Smoking (Yes/No) | 9/11 | 10/10 | .752 |
| Surgery (Yes/No) | 6/14 | 7/13 | .736 |

G = glucose, SM = Shenmai.

1 Unpaired t test.

2 \( \chi^2 \) test.

3 Fischer exact test.

### Table 2

| Variables of coronary artery disease and ejection fraction. | SM (n = 20) | G (n = 20) | P |
|---|---|---|---|
| Number of CAD | 8 | 7 | .885 |
| 1 LAD\(^{†} \) | 6 | 9 | | |
| 2 Vessels\(^{†} \) | 6 | 4 | | |
| 3 Vessels\(^{†} \) | 4.50 ± 9.1 | 45.2 ± 8.8 | .944 |

CABG = coronary artery disease, EF = ejection fraction, G = glucose, LAD = left anterior descending artery, SM = Shenmai.

\(^{†} \) Independent sample t test.

\(^{a} \) Mann–Whitney U test.
Systemic inflammatory response may be caused by surgical trauma, blood contacting foreign body on the surface of cardiopulmonary bypass devices, and ischemia-reperfusion injury. After surgery, the clinical manifestations were fever, leukocytosis, increased capillary permeability, leading to serious injury. After surgery, the clinical manifestations were fever, leukocytosis, increased capillary permeability, leading to serious injury. After surgery, the clinical manifestations were fever, leukocytosis, increased capillary permeability, leading to serious injury. After surgery, the clinical manifestations were fever, leukocytosis, increased capillary permeability, leading to serious injury. After surgery, the clinical manifestations were fever, leukocytosis, increased capillary permeability, leading to serious injury. After surgery, the clinical manifestations were fever, leukocytosis, increased capillary permeability, leading to serious injury. After surgery, the clinical manifestations were fever, leukocytosis, increased capillary permeability, leading to serious injury. After surgery, the clinical manifestations were fever, leukocytosis, increased capillary permeability, leading to serious injury. After surgery, the clinical manifestations were fever, leukocytosis, increased capillary permeability, leading to serious injury. After surgery, the clinical manifestations were fever, leukocytosis, increased capillary permeability, leading to serious injury. After surgery, the clinical manifestations were fever, leukocytosis, increased capillary permeability, leading to serious injury. After surgery, the clinical manifestations were fever, leukocytosis, increased capillary permeability, leading to serious injury. After surgery, the clinical manifestations were fever, leukocytosis, increased capillary permeability, leading to serious injury. After surgery, the clinical manifestations were fever, leukocytosis, increased capillary permeability, leading to serious injury. After surgery, the clinical manifestations were fever, leukocytosis, increased capillary permeability, leading to serious injury. After surgery, the clinical manifestations were fever, leukocytosis, increased capillary permeability, leading to serious injury. After surgery, the clinical manifestations were fever, leukocytosis, increased capillary permeability, leading to serious injury.

In summary, patients receiving coronary artery bypass surgery have poor cardiac functions. Under surgical and anesthetic stress, cardiac functions are significantly inhibited, which need drugs to enhance the tolerance of surgery and anesthesia. SM injection can improve the values of CO, SV, and EF in patients during OPCABG, which are of great significance in maintaining hemodynamic stability and prognosis of myocardial protection. The molecular mechanisms of SM injection in improving cardiac

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### Table 3

**Effects of hemodynamics and CO, SV, and EF (x ± s).**

|                     | t1    | t2    | t3    | t4    | t5    | t6    |
|---------------------|-------|-------|-------|-------|-------|-------|
| SBP, mmHg†          |       |       |       |       |       |       |
| SM                  | 140.6 ±12.35 | 120.5 ±11.16 | 118.1 ±10.22 | 108.5 ±9.12 | 115.2 ±8.17 | 120.3 ±8.12 |
| G                   | 142.4 ±11.28 | 121.6 ±12.13 | 106.7 ±9.24 | 107.6 ±8.15 | 113.2 ±10.21 | 121.5 ±9.11 |
| DBP, mmHg†          |       |       |       |       |       |       |
| SM                  | 95.6 ±9.32 | 88.9 ±5.66 | 85.4 ±5.66 | 70.5 ±5.31 | 75.2 ±7.81 | 80.3 ±8.36 |
| G                   | 96.5 ±9.43 | 89.3 ±6.65 | 70.3 ±6.37 | 70.6 ±6.52 | 76.3 ±7.92 | 81.2 ±8.23 |
| HR, bpm‡            |       |       |       |       |       |       |
| SM                  | 85.1 ±11.0 | 78.2 ±9.1 | 69.2 ±8.5 | 65.3 ±10.2 | 66.5 ±8.6 | 68.2 ±7.6 |
| G                   | 89.1 ±11.9 | 78.9 ±8.8 | 74.8 ±8.9 | 77.2 ±8.8 | 67.3 ±9.6 | 69.3 ±8.4 |
| CO, L/min†          |       |       |       |       |       |       |
| SM                  | 3.16 ±0.75 | 3.22 ±0.85 | 4.0 ±0.56 | 4.6 ±0.67 | 4.72 ±0.56 | 5.02 ±0.52 |
| G                   | 3.15 ±1.12 | 3.23 ±0.92 | 3.30 ±0.88 | 3.41 ±0.98 | 4.01 ±0.66 | 4.13 ±0.72 |
| SV, mL/s†           |       |       |       |       |       |       |
| SM                  | 60.40 ±7.68 | 64.23 ±5.12 | 70.24 ±6.12 | 81.21 ±5.32 | 84.25 ±8.12 | 88.4 ±8.06 |
| G                   | 60.21 ±6.85 | 63.47 ±6.02 | 64.02 ±7.14 | 65.31 ±8.11 | 70.26 ±5.23 | 72.53 ±9.15 |
| EF, %               |       |       |       |       |       |       |
| SM                  | 45.0 ±9.1 | 44.5 ±8.7 | 51.9 ±7.6 | 52.2 ±5.5 | 52.5 ±8.1 | 53.3 ±8.2 |
| G                   | 45.2 ±8.8 | 43.6 ±7.9 | 45.3 ±7.2 | 46.2 ±6.3 | 48.6 ±7.0 | 48.8 ±8.1 |

† P < .05: comparison within the group at the time t1. ANOVA = analysis of variance, CO = cardiac output, DBP = diastolic blood pressure, EF = ejection fraction, G = glucose, HR = heart rate, OPCABG = off-pump coronary artery bypass graft, SBP = systolic blood pressure, SM = Shenmai, SV = stroke volume.

Reprinted ANOVA, comparison between groups.

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**Figure 1.** The values of CO, SV, and EF. (A) The values of CO in the SM group and the G group at t1, t2, t3, t4, t5, and t6. (B) The values of SV in the SM group and the G group at t1, t2, t3, t4, t5, and t6. (C) The values of EF in the SM group and the G group at t1, t2, t3, t4, t5, and t6. CO = cardiac output, EF = ejection fraction, G = glucose, SM = Shenmai, SV = stroke volume.
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References
[1] Kappetein AP, Feldman TE, Mack MC, et al. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. Eur Heart J 2011;32:2125–34.
[2] Arayawudikul N, Sakboon B, Cheewinmetasiri J, et al. Preliminary report of off-pump coronary artery bypass grafting (OPCABG) at Lampang Hospital. Thai J Surg 2014;33:6.
[3] Song Y. Clinical study on off-pump coronary artery bypass grafting in 308 elderly patients with coronary heart disease. Chin J Arteriosclerosis 2014;22:72–4.
[4] Song Y, Li R, Gu XH, et al. Effects of blood washing and autotransfusion during cardiopulmonary bypass on erythrocyte immune and kidney function. Nat Med J China 2006;86:2293–6.
[5] Ueda Y, Torrianni MW, Coppin CM, et al. Antigen cleaning from porcine heart valves with preservation of structural integrity. Int J Artif Organs 2006;29:781–9.
[6] Shi LW, Xie YM, Liao X, et al. Shenmai injection as an adjuvant treatment for chronic cor pulmonale heart failure: a systematic review and meta-analysis of randomized controlled trials. BMC Complement Altern Med 2013;15:418–29.
[7] Wang L, Huang X-E, Cao J. Clinical study on safety of cantharidin sodium and Shenmai injection combined with chemotherapy in treating patients with breast cancer postoperatively. Asian Pac J Cancer Prev 2014;15:5397–600.
[8] Yao N, Chen N, Xu X, et al. Protective effect of Shenmai injection on knee articular cartilage of osteoarthritic rabbits and IL-1beta-stimulated human chondrocytes. Exp Ther Med 2017;13:3013–20.
[9] Liang JC, Huang J. Progress of Shenmai injection in clinical application in cardiovascular disease. China Pract Med 2006;1:48–9.
[10] Huang AJ. Shenmai injection treatment of 32 patients with acute myocardial infarction. J Emergency Tradit Chin Med 2006;25:39–40.
[11] Hao R, Chen YJ, Huang QF. The effect of Shenmai injection on acute hypoxia-oxygen recovery cardiomyocyte apoptosis. Chin J Pathophysiol 2005;21:1524–7.
[12] Hao R, Lou JL, Zhang YL, et al. The effect of Shenmai injection on cardiomyocyte apoptosis after hypoxia. Chin J Pathophysiol 2007;23:660–3.
[13] Hao R, Lou JL, Zhang YL, et al. The influence on the cardiac troponin T of autonomous circulatory resuscitated rabbit after the treatment of Shenmai injection. J Clin Emergency Call 2007;8:57–60.
[14] Cao XD, Ding ZS, Chen JZ. The research progress of Shenmai injection on the pharmacological and clinical. Chin J Inform Tradit Chin Med 2010;33:1253–5.
[15] Hu DR, Jiang H, Peng JH, et al. Regulation of Shenmai injection on immune function of the patients with cardiac valve replacement. Chin J Extracorporeal Circ 2003;1:202–5.
[16] Tian YC, Bai BJ, Wan LF. The effect of Shenmai injection on pump coronary artery bypass grafting in patients with cardiac function. Strait Pharm J 2015;27:152–3.
[17] Li P, Xiong F, Fu Q, et al. Effect of Shenmai injection on arrhythmia rats with myocardial ischemia-reperfusion injury. Chin J Hosp Pharm 2005;25:815–7.
[18] Gao HW, Zheng Z, Hu ST, et al. Risk factors for mortality in coronary artery bypass grafting: analysis of the database from a single center of China. Chin J Clin Thorac Cardiovasc Surg 2007;14:321–5.
[19] Chen GH, Ma ZY, Che L, et al. Protective effect of Shenmai injection on cardiomyocyte apoptosis in elderly coronary heart disease patients receiving total intravenous anesthesia operation. J Guangzhou Univ Tradit Chin Med 2014;31:178–82.
[20] Zhang YM. Clinical effects for the patients with coronary heart disease and angina pectoris by traditional integrated western medicine. Zhejiang J Tradit Chin Med 2013;48:55–7.
[21] Ma RG, Wang CX, Shen YH, et al. Effect of Shenmai injection on ventricular diastolic function in patients with chronic heart failure: an assessment by tissue Doppler imaging. Chin J Inter Med 2010;16:173–5.
[22] Lin L, Wang L, Chen F, et al. Effect and significance of Shenmai injection on value of vascular endothelial active factors of heart valve replacement patients. Tradit Chin Med 2009;34:115–8.
[23] Long MZ, Wang DB, Yang JM. Clinical study on effect of Shenmai injection in treating congestive heart failure. Chin J Integr Tradit Western Med 2003;23:808–10.
[24] Ding F, Shi QP, Jiang XD, et al. Predictive analysis on Shenmai injection-induced adverse reactions with Logistic and ROC curve. Tradit Chin Med 2015;40:1404–9.