**Effect of Xuebijing injection on myocardium during cardiopulmonary bypass: A prospective, randomized, double blind trial**

Zhe-Hao Jin, Xiao-Qing Zhao, Hai-Bin Sun, Jing-Li Zhu, Wei Gao

**Abstract**

**BACKGROUND**
Cardiopulmonary bypass (CPB) is an essential procedure for maintaining the blood supply to vital organs in patients undergoing cardiac surgery. However, perioperative cardiac injury related to CPB remains a severe complication in these patients. Cardiac protection is important for patients undergoing CPB.

**AIM**
To evaluate the potential cardioprotective efficacy of the Chinese medicine preparation Xuebijing injection (XBJ) in patients undergoing CPB.

**METHODS**
Sixty patients undergoing cardiac surgery with CPB were randomly allocated to the XBJ and control groups (saline). XBJ was administered intravenously three times: 12 h prior to surgery, at the beginning of the surgery, and 12 h after the second injection. Cardiac function was evaluated by echocardiography 48 h after surgery. Circulating inflammation- and oxidative-stress-related markers were measured. Clinical outcomes related to intensive care unit (ICU) stay were recorded.

**RESULTS**
Compared to control treatment, XBJ was associated with improved PaO$_2$/FiO$_2$ and cardiac systolic function, but reduced troponin I and creatine kinase fraction after surgery (all $P < 0.05$). The circulating concentrations of tumor necrosis factor-α, interleukin (IL)-1β and IL-8 in the XBJ group were significantly lower than those in the control group (all $P < 0.05$), whereas the circulating concentration of IL-10 was significantly higher in the XBJ group ($P < 0.05$). In addition, the lengths of ICU stay and hospitalization after surgery tended to be shorter in the XBJ group than in the control group, although the differences were not significant.
CONCLUSION

Perioperative administration of XBJ was associated with attenuated cardiac injury during CPB, likely via anti-inflammatory and antioxidative mechanisms.

Key Words: Xuebijing injection; Cardiopulmonary bypass; Cardiac injury; Cardioprotection; Circulating inflammation; Oxidative stress

INTRODUCTION

Cardiopulmonary bypass (CPB) is an essential procedure for maintaining the blood supply to vital organs in patients undergoing cardiac surgery[1]. However, perioperative cardiac injury related to CPB remains a severe complication in these patients[2]. Clinically, there are multiple risk factors for CPB-related cardiac injury, including type of surgery, pattern of CPB induction, and application of cardio-plessia and hypothermia[3]. Pathophysiologically, ischemia-reperfusion injury (IRI) and inflammatory injury induced by CPB have been recognized as the most important mechanisms underlying the pathogenesis of CPB-related cardiac injury[1,4]. Patients who experience cardiac injury during CPB have a poor prognosis[5]. Therefore, identification of novel prevention and treatment strategies for CPB-related cardiac injury is of significant importance in clinical practice.

Xuebijing injection (XBJ), a traditional Chinese drug injection, has been applied for many critical clinical conditions related to the inflammatory response, such as pneumonia, sepsis, inflammatory lung injury, and disseminated intravascular coagulation due to its anti-inflammatory and antioxidative actions[6,7]. Moreover, clinical observations have confirmed the protective role of XBJ for multiple organs during inflammatory injury, including acute sepsis-related lung injury and liver injury[8-10]. In view of the important role of inflammation and oxidative stress in the process of CPB-related cardiac injury, we hypothesized that XBJ may attenuate myocardial injury during the CPB process. We aimed to evaluate the potential efficacy of XBJ on cardiac injury during CPB in these patients in a prospective, randomized, double blinded trial.

MATERIALS AND METHODS

Ethical considerations

The protocol for the present study was approved by the Ethics Committee of the Second Affiliated Hospital of Harbin Medical University before the performance of the study. A predefined study protocol was registered with the Chinese Clinical Trial Registry (ChiCTR-TRC-14004628). Written informed consent forms were signed by all of the included patients before enrollment.

Inclusion criteria and study medications

Sixty patients who underwent cardiac surgery with CPB in our center between November 1, 2018 and February 1, 2019 were included. Patients were randomized to the XBJ group or the control group via a protocol similar to that reported in a previous study[11]. A total of 60 balls, which were marked 0 or 1,
were kept in a black box. When the patient was prepared for surgery, the anesthetist performed the randomization by choosing a random ball from the box, with 0 and 1 indicating saline and XBJ treatments, respectively. Patients who had severe lung dysfunction or infection, pulmonary hypertension, hypoproteinemia, hepatic or renal dysfunction, or a coagulation disorder were excluded from this study. For the 30 patients allocated to the XBJ group, XBJ for injection via photophoric infusion (100 mL, Tianjin Chase Sun Pharmaceutical Group, Tianjin, China)\(^{11}\) was administered 12 h before surgery, at the beginning of the surgery and 12 h after the second injection. For the other 30 patients allocated to the control group, intravenous infusions of saline (100 mL) were applied at the same time points, both via photophoric infusion (Qiaopai Group, Zibo, Shandong, China). An anesthesiologist who was not aware of the allocation performed the anesthesia for all patients. To minimize the influence of the operation on the outcomes in this study, all surgeries were performed by the same surgical team (Figure 1).

**Anesthesia and CPB process**

The standardized anesthesia and operative procedures were administered for all patients. Angiotensin-converting enzyme inhibitors and angiotensin II antagonists were discontinued before surgery, while the other preoperative cardiac medications were administered until the morning of surgery. Midazolam (0.2 mg/kg) was orally administered to the patients 30 min before the operation. In the operating room, a peripheral vein was cannulated, and a mixture of crystal and colloidal solution (1:2) was injected at 8 mL/kg/h. A radial artery of each patient was cannulated to monitor blood pressure and for arterial blood gas analysis. Anesthesia was induced with combined application of lidocaine (1 mg/kg), fentanyl (10 μg/kg), picrocurum (0.05 mg/kg), and etomidate (0.2 mg/kg). After intubation, the right internal carotid artery was cannulated to monitor the central venous pressure (CVP) and for cardiac drug infusion. Volume-controlled ventilation (fraction of inspired oxygen 80% ± 5%, tidal volume 8 mL/kg, respiratory rate 10–12 /min, inspiratory to expiratory ratio 1:2) was applied as the model of mechanical ventilation before CPB. The anesthesia was maintained with sevoflurane (1.5%) and fentanyl (10 μg/kg/h) and changed to propofol (5 mg/kg/h) and fentanyl during CPB before being returned to sevoflurane and fentanyl. The surgical procedure was performed with the pH, arterial CO2 tension (Pa CO\(_2\)), and arterial oxygen tension (PaO\(_2\)) maintained within ranges of 7.35–7.45, 35–40 mmHg, and > 150 mmHg, respectively.

After surgery, all of the patients were observed in the intensive care unit (ICU), where the third injection of XBJ or saline was applied. The standard cardiovascular medications and mechanical ventilation support were applied as needed. Weaning from the ventilator was attempted if the patients were considered hemodynamically and respiratory stable according to the following parameters: PaO\(_2\) /FiO\(_2\) ratio > 200 mmHg, acid–base balance, chest drainage < 80 mL/h, and body temperature ≥ 36°C.

**Arterial blood gas analysis**

Arterial blood gas analysis was performed before the first injection of XBJ (baseline) and 0, 12, 24 and 48 h after the surgery. The PaO\(_2\)/FiO\(_2\) ratio was calculated. Peripheral blood samples were collected at the same time points.

**Measurement of markers of cardiac injury, inflammation, and oxidative stress**

Troponin (TnI) and creatine kinase fraction MB (CKMB) concentrations in serum were determined using ELISA (Boster, Wuhan, China). Markers of inflammation, including serum concentrations of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-8, and IL-10 were also measured with ELISA (Sigma–Aldrich, St. Louis, MO, United States). We also determined the circulating levels of 8-isoprostane (Cayman Chemicals, Ann Arbor, MI, United States) and malondialdehyde (MDA) (Nanjing Jiancheng, Nanjing, China) as markers of oxidative stress using commercial kits.

**Outcomes**

The primary outcome of the study was the change in TnI value from the beginning of anesthesia to 48 h after surgery. In addition, the incidences of clinical outcomes including myocardial infarction, cardiac stunning, acute respiratory distress syndrome (ARDS), and acute kidney injury (AKI) were recorded.

**Sample size calculation**

To detect a 2 ng/mL reduction in TnI within 48 h after surgery between two groups, a total of 50 patients are needed with a power of 80% and an α level of 0.05. We included 30 patients in each group (rather than 25) after assuming the potential rate of loss during follow-up.

**Statistical analyses**

Continuous data that were normally distributed were presented as mean ± SD and compared with the independent t test. Data for categorical variables were presented as numbers and proportions, and these data were compared via Chi-square analysis. For continuous variables that were measured at multiple time points, repeated-measures analysis of variance was applied with Bonferroni’s correction as post hoc analysis. P < 0.05 was considered statistically significant. We used SPSS software (Chicago, IL, United
RESULTS

In the present study, a total of 60 patients were enrolled, and no patient was excluded. All the patients were successfully weaned from CPB and transferred to the ICU. There were no significant differences in the demographic data between the XBJ and control groups (Table 1). In addition, no significant differences were found regarding the characteristics of CPB and surgery, including CPB time, aortic cross clamp time, surgical duration, and quantity of potassium cardioplegic solution used. Patients from the XBJ and control groups received a similar volume of perioperative fluid infusion, had similar urine volumes, and consumed similar amounts of vasoactive medications during the surgery (P > 0.05, Table 1).

Although the serum concentrations of TnI and CK-MB were comparable between patients in the two groups at baseline (P > 0.05), the serum concentrations of both biomarkers of cardiac injury were elevated in both groups after surgery. However, the serum concentrations of TnI and CK-MB were significantly lower in patients in the XBJ group than in those in the saline group after surgery (P < 0.05).

The perioperative hemodynamic variables, including mean arterial pressure (MAP) and CVP, were similar between the two groups. There also were no significant differences in the results of arterial blood analysis between the two groups except for \( \text{PaO}_2/\text{FiO}_2 \), which was increased significantly from 12 to 72 h after surgery in the XBJ group compared with the levels in the control group (P < 0.05, Table 2). Although the baseline ejection fraction in patients from both groups was similar, the ejection fraction after surgery was significantly higher in the XBJ group than in the control group (P < 0.05, Table 2). In addition, treatment with XBJ was associated with a significantly shorter length of ICU stay and time from operation to discharge compared with those in the saline group (both P < 0.05, Table 2).

Compared with those at baseline, all serum biomarker levels were increased significantly in the two groups. The circulating concentrations of TNF-\( \alpha \), IL-1\( \beta \) and IL-8 in the XBJ group were significantly lower than those in the control group (all P < 0.05, Table 3), whereas the circulating concentration of IL-10 was significantly greater in the XBJ group (P < 0.05, Table 3). No severe complications such as myocardial infarction, acute kidney failure, cerebrovascular accidents, or mortality were found during ICU stay.

DISCUSSION

In the present study, we found that XBJ significantly reduced myocardial injury in patients undergoing CPB, as demonstrated by the significantly lower levels of markers of myocardial injury, including TnI and CK-MB, as well as the preserved cardiac ejection fraction in patients in the XBJ group as compared with those in the control group. The benefit of XBJ against myocardial injury was accompanied by reduced serum concentrations of inflammatory markers, including TNF-\( \alpha \), IL-1\( \beta \) and IL-8, and an increase in the concentration of the anti-inflammatory factor IL-10. These results suggest that periop-
Table 1 Baseline characteristics of patients allocated to the Xuebijing injection and control (saline) groups

|                          | Saline group (n = 30) | XBJ group (n = 30) | P value |
|--------------------------|-----------------------|--------------------|---------|
| Age (yr)                 | 57.4 ± 5.3            | 56.8 ± 6.2         | 0.69    |
| Male                     | 18                    | 20                 |         |
| Weight (kg)              | 63.6 ± 5.8            | 65.4 ± 5.6         | 0.22    |
| Diabetes mellitus (n)    | 5                     | 7                  | 0.44    |
| Preoperative LVEF (%)    | 51.7 ± 8.5            | 52.5 ± 7.6         | 0.71    |
| Ejection fraction        | 50.2 ± 3.2            | 50.3 ± 3.8         | 0.91    |
| Preoperative medications (n) |                      |                    |         |
| β-blockers               | 8                     | 6                  | 0.54    |
| Calcium channel blockers | 5                     | 7                  | 0.52    |
| Renin angiotensin system inhibitors | 5 | 3  | 0.44 |
| Statin                   | 4                     | 2                  | 0.39    |
| Digoxin                  | 6                     | 8                  | 0.54    |
| Diuretics                | 16                    | 19                 | 0.43    |
| Surgical procedure (n)   | Aortic valve replacement | 8               | 11   | 0.40 |
|                          | Mitral valve replacement | 10               | 9    | 0.78 |
|                          | Tricuspid annuloplasty | 12                 | 10    | 0.59 |
| Pulmonary function test  | FVC; % predicted       | 82.8 ± 7.4         | 81.9 ± 8.1 | 0.65 |
|                          | Operation time (min)   | 257 ± 38           | 271 ± 41 | 0.17 |
|                          | CPB time (min)         | 104 ± 31           | 111 ± 27 | 0.35 |
|                          | Intraoperative fluid balance (mL) | 2138 ± 348 | 2215 ± 387 | 0.42 |

Data are expressed as mean ± SD (normally distributed data) or median (interquartile range). Chi-square analysis was used for categorical variables, independent t test for normally distributed data. FVC: Forced vital capacity; LVEF: Left ventricular ejection fraction; XBJ: Xuebijing injection.

Table 2 Comparison of postoperative outcomes between the Xuebijing injection and control (saline) groups

|                          | Saline group (n = 30) | XBJ group (n = 30) | P value |
|--------------------------|-----------------------|--------------------|---------|
| Ejection fraction (day 2)| 42.2 ± 2.7            | 46.3 ± 3.7         | 0.001   |
| Mechanical ventilation time (h) | 10.5 ± 2.6            | 8.9 ± 1.7          | 0.006   |
| Length of ICU stay (h)   | 31.6 ± 5.2            | 28.9 ± 4.4         | 0.034   |
| Time from surgery to discharge (d) | 12.5 ± 3.8            | 10.7 ± 2.6         | 0.032   |
| ARDS (n)                 | 3                     | 4                  | 0.687   |

Data are expressed as mean ± SD (normally distributed data) or median (interquartile range). Chi-square analysis was used for categorical variables, independent t test for normally distributed data. ARDS: acute respiratory distress syndrome; ICU: Intensive care unit; XBJ: Xuebijing injection.

Operative administration of XBJ is associated with attenuated cardiac injury during the CPB process, likely via anti-inflammatory and antioxidative mechanisms.

During the process of CPB and cardiac surgery, systemic inflammation and ischemia/reperfusion induced by these procedures contribute to cardiac injury[12,13]. Previous studies showed that myocardial injury is an independent risk factor for poor prognosis among patients who undergo cardiac surgery[5,14]. Although some agents have been proposed to exert a cardiac protective role in CPB, novel preventive agents targeting multiple potential mechanisms of CPB-related myocardial injury remain to be developed[15,16]. XBJ had been shown to exert a therapeutic effect against systemic inflammation in
In the present study, we found that XBJ significantly decreased the postoperative serum TnI and CK-MB levels in patients undergoing CPB. These results confirmed that XBJ can attenuate local and systemic inflammation and improve postoperative respiratory function in patients undergoing CPB. In addition, XBJ also preserved the cardiac output postoperatively. These results indicate that XBJ ameliorated cardiac injury and improved cardiac function after CPB. Our previous clinical study demonstrated that XBJ attenuated local and systemic inflammation and improves the postoperative respiratory function in patients undergoing CPB[11]. These results confirmed the anti-inflammatory activity of XBJ in patients undergoing CPB. Because inflammation plays a key role in the pathogenesis of cardiac injury during CPB, we hypothesized that perioperative application of XBJ could at least attenuate cardiac injury after CPB. This hypothesis was confirmed by the present findings of significantly lower levels of markers of myocardial injury, including TnI and CK-MB, and preserved cardiac ejection fraction in patients in the XBJ group compared with those in the control group.

In addition to CBP-induced systemic inflammation, the cardiac surgery itself may also directly cause myocardial injury, which also can be represented by elevated serum levels of TnI and CK-MB[17-19]. In the present study, we found that XBJ significantly decreased the postoperative serum TnI and CK-MB levels. Moreover, XBJ also preserved the cardiac output postoperatively. These results indicate that XBJ ameliorated cardiac injury and improved cardiac function after CPB. Our previous study showed that XBJ reduced the levels of pro-inflammatory factors such as TNF-α, IL-1, IL-6, and IL-8, influences postoperative morbidity and mortality[1]. TNF-α and IL-1 are early mediators of inflammation as they initiate the local inflammatory response [20], while other inflammatory factors such as IL-6 and IL-8 are believed to contribute to systemic inflammation after CPB. A strong association between inflammatory cytokine levels and adverse clinical outcomes after CPB has been observed[21]. Increased levels of IL-6 and IL-8 have been proven to be positively correlated with TnI level, myocardial injury and mortality after CPB[21,22]. In the present study, we found that XBJ significantly reduced the levels of pro-inflammatory factors after CPB, which is consistent with our previous studies[7,9,11]. We also found that XBJ increased the level of the anti-inflammatory factor IL-10. A previous study showed that XBJ may regulate the inflammatory response via its inhibition of nuclear factor (NF)-κB[23]. However, the exact mechanism underling the potential regulatory effects of XBJ on the inflammatory response remain to be determined.

In addition to inflammation, the production of reactive oxygen species (ROS) induced by IRI has been considered an important contributor to cardiac injury during CPB[4,24]. Previous studies suggested that the cardiac injury resulted from ROS initiation of local cardiac inflammation, which then led to further...
oxidative-stress-mediated heart injury[25,26]. It has been confirmed that the circulating level of 8-isoprostane, the final product of lipid peroxidation, correlates directly with the tissue damage caused by ROS. The circulating level of 8-isoprostane has been shown to be a reliable indicator of cardiac oxidative stress in myocardial infarction[27] as well as coronary reperfusion[28], and this relationship is also associated with the elevation of TnI[28]. In the present study, we found the XBJ significantly decreased the serum levels of 8-isoprostane and MDA, and these results were consistent with previous studies[29,30], which demonstrated the potential antioxidative efficacy of XBJ. The mechanisms underlying the antioxidative efficacy of XBJ were proposed to be related to its regulation of the inducible nitric oxide synthase, superoxide dismutase[29] and oxidized glutathione activity[29].

Our study had some limitations. We have not observed long-term results, and we have not discussed in depth the mechanism of action of the drug.

CONCLUSION
The results of our study indicate that perioperative administration of XBJ is associated with attenuated cardiac injury during CPB, and this effect is likely the result of the anti-inflammatory and antioxidative activities of XBJ.

ARTICLE HIGHLIGHTS

Research background
Cardiopulmonary bypass (CPB) provides good perioperative protection for patients undergoing cardiac surgery. However, perioperative cardiac injury related to CPB remains a severe complication in these patients and affects their prognosis.

Research motivation
Inflammation and oxidative stress play an important role in the CPB-related heart injury, and clinical observations have confirmed the protective effect of Xuebijing injection (XBJ) on multiple organs against inflammatory damage.

Research objectives
To evaluate the potential efficacy of XBJ on cardiac injury during CPB.

Research methods
Sixty patients who underwent cardiac surgery with CPB in our center between November 1, 2018 and February 1, 2019 were included. XBJ was injected intravenously 3 times: 12 h before the operation, at the beginning of the operation, and 12 h after the second injection. The heart function was assessed by echocardiography 48 h after the operation. Markers related to circulatory inflammation and oxidative stress were measured and clinical results at intensive care unit (ICU) were recorded.

Research results
All the 60 patients were successfully weaned from CPB and transferred to the ICU. Compared to the control group, XBJ improved PaO2/FiO2 and cardiac systolic function, but reduced troponin I and creatine kinase fraction after surgery (all P < 0.05). Moreover, the circulating concentrations of TNF-α, IL-1β and IL-8 in the XBJ group were significantly lower than those in the control group (all P < 0.05), whereas the circulating concentration of IL-10 was significantly higher in the XBJ group (P < 0.05). In addition, the lengths of ICU stay and hospitalization after surgery tended to be shorter in the XBJ group than in the control group, although the differences were not statistically significant.

Research conclusions
Perioperative administration of XBJ was associated with attenuated cardiac injury during the CPB surgery, likely via anti-inflammation– and anti-oxidation-related mechanisms.

Research perspectives
Further research is required with more meaningful data to accurately evaluate the efficacy of XBJ on cardiac injury during CPB, and clarify the mechanism of action of XBJ.
FOOTNOTES

Author contributions: Jin ZH and Gao W designed the study; Jin ZH and Zhao XQ collected the intraoperative data; Sun HB and Zhu JL collected the postoperative data; Gao W analyzed the data and Jin ZH wrote the paper.

Institutional review board statement: The protocol for the present study was approved by the ethics committee of the Second Affiliated Hospital of Harbin Medical University before the performance of the study (HMUIRB20140012).

Clinical trial registration statement: A predefined study protocol was registered with the Chinese Clinical Trial Registry (ChiCTR-TRC-14004628).

Informed consent statement: An informed consent form was signed by each patient or their legal guardian before enrollment.

Conflict-of-interest statement: All authors have no any conflicts of interest.

Data sharing statement: No additional data are available.

CONSORT 2010 statement: The authors have read the CONSORT 2010 statement, and the manuscript was prepared and revised according to the CONSORT 2010 statement.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: China

ORCID number: Zhe-Hao Jin 0000-0002-5413-9935; Xiao-Qing Zhao 0000-0002-5052-3577; Hai-Bin Sun 0000-0003-1692-9087; Jing-Li Zhu 0000-0001-8918-7534; Wei Gao 0000-0001-5748-899X.

S-Editor: Ma YJ
L-Editor: A
P-Editor: Ma YJ

REFERENCES

1 Paparella D, Yau TM, Young E. Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update. Eur J Cardiothorac Surg 2002; 21: 232-244 [PMID: 11825729 DOI: 10.1016/s1074-2484(11)410318]

2 Biccard BM. Detection and management of perioperative myocardial ischemia. Curr Opin Anaesthesiol 2014; 27: 336-343 [PMID: 24670983 DOI: 10.1097/ACO.0000000000000711]

3 Ngaage DL, Cowen ME, Cale AR. Cardiopulmonary bypass and left ventricular systolic dysfunction impacts operative mortality differently in elderly and young patients. Eur J Cardiothorac Surg 2009; 35: 235-240 [PMID: 19084419 DOI: 10.1016/j.ejcts.2008.10.043]

4 Mentzer RM Jr. Myocardial protection in heart surgery. J Cardiovasc Pharmacol Ther 2011; 16: 290-297 [PMID: 21821531 DOI: 10.1177/1074248411410318]

5 Paparella D, Guida P, Caparrotti S, Fanelli V, Martinelli G, Mazzei V, Zaccaria S, Biscoglia L, Scrascia G. Myocardial damage influences short- and mid-term survival after valve surgery: a prospective multicenter study. J Thorac Cardiovasc Surg 2014; 148: 2373-2379.e1 [PMID: 24290712 DOI: 10.1016/j.jtcvs.2013.10.061]

6 Yin Q, Li C. Treatment effects of xuebijing injection in severe septic patients with disseminated intravascular coagulation. Evid Based Complement Alternat Med 2014; 2014: 949254 [PMID: 24778706 DOI: 10.1155/2014/949254]

7 Qi F, Liang ZX, She DY, Yan GT, Chen LA. A clinical study on the effects and mechanism of xuebijing injection in severe pneumonia patients. J Tradit Chin Med 2011; 31: 46-49 [PMID: 21563507 DOI: 10.1016/j.jtcvm.2013.10.061]

8 He XD, Wang Y, Wu Q, Wang HX, Chen ZD, Zheng RS, Wang ZS, Wang JB, Yang Y. Xuebijing Protects Rats from Sepsis Challenged with Acinetobacter baumannii by Promoting Annexin A1 Expression and Inhibiting Proinflammatory Cytokines Secretion. Evid Based Complement Alternat Med 2013; 2013: 804940 [PMID: 24369483 DOI: 10.1155/2013/804940]

9 Sun J, Xue Q, Guo L, Cui L, Wang J. Xuebijing protects against lipopolysaccharide-induced lung injury in rabbits. Exp Lung Res 2010; 36: 211-218 [PMID: 20426529 DOI: 10.3109/01902140903312125]

10 Li D, Lu L, Zhang J, Wang X, Xing Y, Wu H, Yang X, Shi Z, Zhao M, Fan S, Meng A. Mitigating the effects of Xuebijing injection on hematopoietic cell injury induced by total body irradiation with γ-rays by decreasing reactive oxygen species levels. Int J Mol Sci 2014; 15: 10541-10553 [PMID: 24927144 DOI: 10.3390/ijms150610541]

11 Gao W, Li N, Cui XG. Efficacy of Xuebijing Injection () on Cardiopulmonary Bypass-Associated Pulmonary Injury: A Prospective, Single-center, Randomized, Double Blinded Trial. Chin J Integ Med 2018; 24: 815-821 [PMID: 30062633 DOI: 10.1007/s11655-018-2933-7]
Jin ZH et al. Xuebijing and postoperative cardiac injury

12 Salerno TA. Myocardial protection era: from valve surgery to heart transplantation. *Artif Organs* 2012; 36: 939-942 [PMID: 23121201 DOI: 10.1111/j.1525-1594.2012.01571.x]

13 Steffens S, Montecucco F, Mach F. The inflammatory response as a target to reduce myocardial ischaemia and reperfusion injury. *Thromb Haemost* 2009; 102: 240-247 [PMID: 19652874 DOI: 10.1160/TH08-12-0837]

14 Salis S, Mazzanti VV, Merli G, Salvi L, Tedesco CC, Veglia F, Sisullo E. Cardiopulmonary bypass duration is an independent predictor of morbidity and mortality after cardiac surgery. *J Cardiosurg Vasce Annesth* 2008; 22: 814-822 [PMID: 18948034 DOI: 10.1053/j.jvca.2008.08.004]

15 De Hert S, Moerman A. Myocardial injury and protection related to cardiopulmonary bypass. *Best Pract Res Clin Anaesthesiol* 2015; 29: 137-149 [PMID: 26060026 DOI: 10.1016/j.bpa.2015.03.002]

16 Chambers DJ, Falloul HB. Cardiopulmonary bypass: pharmacological arrest and cardioprotection during global ischemia and reperfusion. *Pharmacol Ther* 2010; 127: 41-52 [PMID: 20398698 DOI: 10.1016/j.pharmther.2010.04.001]

17 Maynard SJ, Menown IB, Adgey AA. Troponin T or troponin I as cardiac markers in ischaemic heart disease. *Heart* 2000; 83: 371-373 [PMID: 10722526 DOI: 10.1136/heart.83.4.371]

18 Kazmi KA, Iqbal SP, Bakr A, Iqbal MP. Admission creatinine kinase as a prognostic marker in acute myocardial infarction. *J Pak Med Assoc* 2009; 59: 819-822 [PMID: 20201171]

19 Robinson DJ, Christensen RH. Creatinine kinase and its CK-MB isoenzyme: the conventional marker for the diagnosis of acute myocardial infarction. *J Emerg Med* 1999; 17: 95-104 [PMID: 9950395 DOI: 10.1016/s0736-4679(98)00129-2]

20 Poon KS, Palanisamy K, Chang SS, Sun KT, Chen KB, Li PC, Lin TC, Li CY. Plasma exosomal miR-223 expression regulates inflammatory responses during cardiac surgery with cardiopulmonary bypass. *Sci Rep* 2017; 7: 10807 [PMID: 28834744 DOI: 10.1038/s41598-017-09709-w]

21 Allan CK, Newburger JW, McGrath E, Elder J, Psoinos C, Laussen PC, del Nido PJ, Wypij D, McGowan FX Jr. The myocardial protection era: from valve surgery to heart transplantation. *Thromb Haemost* 2008; 101: 2606-0026 DOI: 10.1160/TH08-12-0837

22 Holmes JH 4th, Connolly NC, Paull DL, Hill ME, Guyton SW, Ziegler SF, Hall RA. Magnitude of the inflammatory response to cardiopulmonary bypass and its relation to adverse clinical outcomes. *Inflamm Res* 2002; 51: 579-586 [PMID: 12558191] DOI: 10.1007/p100012432

23 Jiang M, Zhou M, Han Y, Xing L, Zhao H, Dong L, Bai G, Luo G. Identification of NF-xB Inhibitors in Xuebijing injection for sepsis treatment based on bioactivity-integrated UPLC-Q/TOF. *Artif Organs* 2013; 147: 426-433 [PMID: 23524166 DOI: 10.1161/j.epj.2013.03.032]

24 Zakkur M, Guida G, Suleiman MS, Angelini GD. Cardiopulmonary bypass and oxidative stress. *Oxid Med Cell Longe* 2015; 1989863 [PMID: 25722792 DOI: 10.1155/2015/189863]

25 Anselmi A, Abbate A, Girola F, Nasso G, Biondi-Zoccai GG, Possati G, Gaudino M. Myocardial ischemia, stunning, inflammation, and apoptosis during cardiac surgery: a review of evidence. *EUR J Cardiovthorac Surg* 2004; 25: 304-311 [PMID: 15019653 DOI: 10.1016/j.ejcts.2003.12.003]

26 Mehlorh U, Krahawinkel A, Geissler HJ, de Rosee K, Fischer UM, Klass O, Suedkamp M, Bloch W. Nitrotyrosine and 8-isoprostane formation indicate free radical-mediated injury in hearts of patients subjected to cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 2003; 125: 178-183 [PMID: 12539002 DOI: 10.1016/j.vtc.2003.07.001]

27 Mehrabi MR, Serbecic N, Ekmekcioglu C, Tamaddon F, Ullrich R, Sinzinger H, Glogar HD. The isoprostane 8-epi-PGF(2alpha) is a valuable indicator of oxidative injury in human heart valves. *Cardiovasc Pathol* 2001; 10: 241-245 [PMID: 11673063 DOI: 10.1016/s0736-4807(01)00084-9]

28 Caputo M, Mokhatri A, Rogers CA, Panayiotou N, Chen Q, Ghorbel MT, Angelini GD, Parry AJ. The effects of normoxic versus hyperoxic cardiopulmonary bypass on oxidative stress and inflammatory response in cyanotic pediatric patients undergoing open cardiac surgery: a randomized controlled trial. *J Thorac Cardiovasc Surg* 2009; 138: 206-214 [PMID: 19577081] DOI: 10.1016/j.jtcvs.2008.12.028]

29 Chen Y, Tong H, Pan Z, Jiang D, Zhang X, Qiu J, Su L, Zhang M. Xuebijing injection attenuates pulmonary injury by reducing oxidative stress and proinflammatory damage in rats with heat stroke. *Exp Ther Med* 2017; 13: 3408-3416 [PMID: 28588676 DOI: 10.3892/etm.2017.4444]

30 Zhao L, Zhou L, Xu T, Li Z, Liu L, Shi Y, Kang J, Gao D, Du S, Sun Z, Zhang X. Antiseptic Activity of Ethnomedicinal Xuebijing Revealed by the Metabolomics Analysis Using UHPLC-Q-Orbitrap HRMS. *Front Pharmacol* 2018; 9: 300 [PMID: 29651245 DOI: 10.3389/fphar.2018.00300]
