71211-Answering Reviewers

Dear Dr Wang,

Thank you very much for your decision letter and advice on our manuscript entitled "Xuebijing Injection attenuates cardiac injury during cardiopulmonary bypass: anti-inflammatory and antioxidant effects".We also thank the reviewers for the constructive comments and suggestions. We have revised the manuscript accordingly, and all amendments are indicated by red font in the revised manuscript. In addition, our point-by-point responses to the comments are listed below this letter.

This revised manuscript has been edited and proofread by "MedE Editing Service"

We hope that our revised manuscript is now acceptable for publication in your journal and look forward to hearing from you soon.

With best wishes,

Yours sincerely,

Zhe-hao Jin

First of all, we would like to express our sincere gratitude to the reviewers for their constructive and positive comments.

Replies to Reviewer 1

Reviewer #1:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: This study entitled "Xuebijing Injection attenuates cardiac injury during cardiopulmonary bypass: anti-inflammatory and antioxidant

effects" seems to have been generally well executed and written. Moreover, I believe that this paper will be of great interest to the readers and therefore, in my opinion, it deserves to be published. I have only a few minor suggestions to improve the quality of the paper. Title Please do not insert the findings of your study in the title. Furthermore, include the type of study in your title, so please rewrite it. Running tile Should be revised (e.g., Xuebijing and postoperative cardiac injury).
Abstract/Background Please replace the sentence with one which is more informative. Introduction Please separate the sentence of your aim and hypothesis into two sentences. Discussion Please addressed the limitations of your study.

1.Title Please do not insert the findings of your study in the title. Furthermore, include the type of study in your title, so please rewrite it.

Response:

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

2.Running title Should be revised (e.g., Xuebijing and postoperative cardiac injury).

Response: Running title:Xuebijing and postoperative cardiac injury

3.Abstract/Background Please replace the sentence with one which is more informative.

Response: 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.

4.Introduction Please separate the sentence of your aim and hypothesis into two sentences.

Response: 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 in these patients in a prospective, randomized, double blinded trial.

5.Discussion Please addressed the limitations of your study.

Response: 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.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: 1-There are typos and grammatical errors that need to be corrected. 2-The authors have to put the statistical methods used in each table legend. 3-As the references are relatively old, please use the new references in the manuscript. 4-The authors should unify the style of references in the text of this manuscript. (e.g., line 335) 5-Please explain in the text of the manuscript how to choose the dose of XBJ?

1.There are typos and grammatical errors that need to be corrected.

Response: The Manuscript has been edited and proofread by "MedE Editing Service" again to crrected the errors.

2.The authors have to put the statistical methods used in each table legend.

Table 1 Baseline characteristics of patients allocated to the XBJ and control (saline) groups

	Saline group (n=30)	**XBJ group (n=30)**	***P***
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 XBJ and control (saline) groups

	Saline group (*n* = 30)	**XBJ group (*n* = 30)**	***P***
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.

Table 3 Comparison of dynamic changes in respiratory function and inflammation- and oxidative stress-related markers during the perioperative periods between the XBJ and control groups

Group		Baseline	0 h	12 h	24 h	48 h
PaO_2/FiO_2	Saline	398.40±22.66	361.92±48.62	258.93±39.03	320.64±46.43	341.44±35.28
	XBJ	387.12±35.77	358.48±39.21	289.40±44.07*	353.34±31.54*	379.08±22.54*
CK-MB	Saline	0.26±0.07	0.71±0.12	2.74±0.48	4.25±0.83	1.95±0.62
	XBJ	0.26±0.08	0.58±0.12	2.27±0.33*	3.02±0.44*	1.09±0.37*
TnI	Saline	0.02±0.01	1.45±0.28	8.01±1.13	13.03±2.56	4.03±0.92
	XBJ	0.02±0.01	1.38±0.93	4.77±0.76*	8.29±1.73*	3.16±0.43*
TNF-α	Saline	13.51±4.19	71.18±29.21	147.36±43.84	226.31±60.22	122.48±55.18
	XBJ	15.61±4.51	70.69±27.24	125.64±34.44*	173.61±40.03*	99.96±33.37*
IL-1β	Saline	16.98±4.14	32.95±9.05	92.31±18.45	78.43±17.54	62.71±15.40
	XBJ	13.13±4.22	28.23±6.24	77.25±9.16*	66.15±12.18*	43.60±13.33*
IL-8	Saline	831.36±136.86	1002.73±180.26	1530.90±235.96	1400.83±268.85	1134.86±211.41
	XBJ	767.30±155.86	960.43±187.49	1369.93±244.21*	1251.76±240.81*	984.86±184.43*
IL-10	Saline	90.60±15.82	121.96±18.15	167.41±18.54	152.53±33.94	121.26±20.73
	XBJ	87.27±20.83	123.30±18.31	176.72±27.91	166.97±21.94*	131.87±19.52*
MDA	Saline	0.11±0.08	0.49±0.19	0.14±0.09	0.11±0.08	0.11±0.10
	XBJ	0.09±0.04	0.31±0.12*	0.13±0.11	0.10±0.06	0.10±0.04
8-Isoprostane	Saline	1.84±0.46	8.31±0.76	6.29±0.75	3.25±0.52	1.83±0.36
	XBJ	2.00±0.55	6.63±0.88*	6.29±0.75	3.24±0.51	1.84±0.53

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. PaO_2: Arterial oxygen tension; FiO_2: Fraction of inspired oxygen;

CK-MB: Creatine kinase isoenzyme MB; TnI: Troponin I; TNF-α: Tumor necrosis factor-α; IL: interleukin; MDA: Malondialdehyde; *: $P < 0.05$

3.As the references are relatively old, please use the new references in the

manuscript.

Response: Correction has been made in the revised manuscript (page 18-23)

The new references have replaced the old references as follows（Reference number of 1，3，4，7，9，13，14，17，18，19，22，26，27，28 have been repalced）

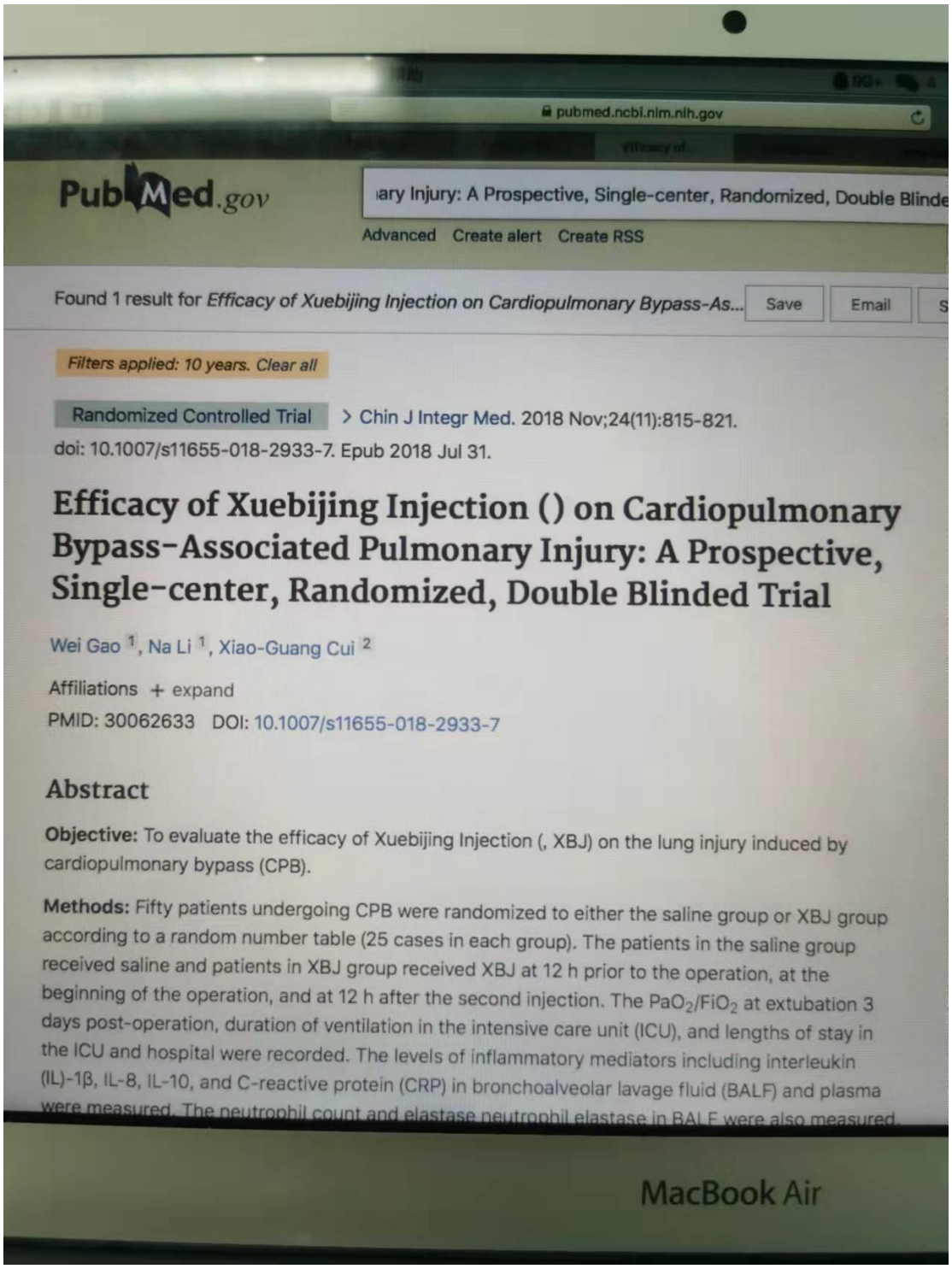
4.The authors should unify the style of references in the text of this manuscript. (e.g., line 335)

Response: Correction has been made in the revised manuscript (page 18-23)

5-Please explain in the text of the manuscript how to choose the dose of XBJ?

Response: XBJ for injection via photophobic infusion (100 ml, Tianjin Chase Sun Pharmaceutical Group, Tianjin, China) according to the instructions of the manufacturer [11] were administered 12 hours before the surgery, at the beginning of the surgery and 12 hours after the second injection.

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 Integr Med 2018; 24: 815-821 [PMID: 30062633 DOI: 10.1007/s11655-018-2933-7]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Chin J Integr Med. 2018 Nov;24(11):815-821.
doi: 10.1007/s11655-018-2933-7. Epub 2018 Jul 31.
Efficacy of Xuebijing Injection () on Cardiopulmonary Bypass-Associated Pulmonary Injury: A Prospective, Single-center, Randomized, Double Blinded Trial
Wei Gao [1], Na Li [1], Xiao-Guang Cui [2]
Affiliations + expand
PMID: 30062633 DOI: 10.1007/s11655-018-2933-7
Abstract
Objective: To evaluate the efficacy of Xuebijing Injection (, XBJ) on the lung injury induced by cardiopulmonary bypass (CPB).
Methods: Fifty patients undergoing CPB were randomized to either the saline group or XBJ group according to a random number table (25 cases in each group). The patients in the saline group received saline and patients in XBJ group received XBJ at 12 h prior to the operation, at the beginning of the operation, and at 12 h after the second injection. The PaO_2/FiO_2 at extubation 3 days post-operation, duration of ventilation in the intensive care unit (ICU), and lengths of stay in the ICU and hospital were recorded. The levels of inflammatory mediators including interleukin (IL)-1β, IL-8, IL-10, and C-reactive protein (CRP) in bronchoalveolar lavage fluid (BALF) and plasma were measured. The neutrophil count and elastase neutrophil elastase in BALF were also measured.
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