Author’s response to reviews

Title: Effects of inhaled nitric oxide for postoperative hypoxemia in acute type A aortic dissection: A retrospective observational study

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Author’s response to reviews:

Dear Editor:

We would like to express our gratitude for another opportunity to submit our research manuscript titled “Effects of inhaled nitric oxide for postoperative hypoxemia in acute type A aortic dissection: A retrospective observational study” for consideration to be published in Journal of Cardiothoracic Surgery. We appreciate the Reviewers’ invaluable comments, which have significantly enriched the revised version of our manuscript. We present explanations and modifications in lieu of these comments in the revised text and provide detailed point-by-point responses to the reviewers’ comments as below.
Thanks for your consideration. We look forward to hearing from you.

Sincerely,

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Reviewer #1:

Thank you very much for giving me this opportunity to check your article. There have been quite a lot of studies on perioperative hypoxemia in patients with aortic dissection, and the treatment of NO has also proven to be an effective treatment. So I have a few questions:

1. In the process of data analysis, you used the statistical method of propensity score, but from the relevant data in Table 1, although the number of patients enrolled in the two groups is quite different, the baseline data is still balanced. Why did you adopt PSM this way later?

Response 1:

Thank you very much for your valuable advices. We believe your suggestions would be very helpful in improving the quality of our article. Most of variables between two groups did not show any significant difference in the baseline except DHCA time and minimum temperature (P=0.041 and P=0.040 respectively). Deep hypothermia circulatory arrest time has been reported to be an independent risk factor of postoperative hypoxemia following Stanford A aortic dissection (Lin N. et al, Interactive Cardiovascular and Thoracic Surgery 24 (2017) 251–256; Wang Y. et al, J Cardiothorac Surg, 2013,8:118). Thus, we must use PSM to balance them, and data after PSM was well balanced. The reason we adopt PSM was increasing comparability of two groups. We also compared all outcomes between the two groups without PSM as a sensitivity analysis and got the same results.

2. In Table 1, there was no statistical difference between the extracorporeal circulation time and the blocking time during the operation. There was only a difference between the deep and low temperature times, but the mean value was only 2 min. I expressed doubts about this data, so please provide the magazine with you. Raw data of the study, again subject to statistical review.

Response 2:
Thank you for the valuable and reasonable suggestion. We have re-reviewed our data, in order to make sure the accuracy of results, and examined by two statisticians of clinical research center of Shanghai Jiao Tong University School of Medicine (See acknowledgement). Because the interquartile range is small, there is also a statistical difference in the small mean difference. We also compared all outcomes between the two groups without PSM as a sensitivity analysis and got the same results (see supplement 1). The data analysis was performed using SPSS 24.0 statistical software (IBM Corp., Armonk, NY, USA). Variables with skewed distribution data are presented as medians and interquartile ranges. Continuous variables were compared using the t-test or Mann-Whitney U-test method. The raw data has also been submitted to editor.

3. The most important thing is that from Tables 1 and 2, the baseline data of patients before and 24 hours after surgery is basically the same, but you did not accurately describe the criteria for enrollment, why only 40 of 174 patients used iNo Treatment, what is the reason?

Response 3:

We are grateful for your detailed comments and suggestions and we believe that would greatly improve our manuscript. Table 1 and 2 presented the characteristics of patients with postoperative hypoxemia which was defined as PaO2/FiO2 \( \leq 200 \) occurring within 24 hours after surgery. As you advised, we have accurately described the criteria for enrollment in the Method part. “The enrollment criteria were as follows: (I) patients who received repairment surgery for AADA; (II) patients with a persistent postoperative hypoxemia, which was defined as the blood gas exam showed that ratio of arterial partial pressure of oxygen (PaO2) to fraction of inspired oxygen (FiO2) was equal to or less than 200 mmHg (PaO2/FiO2 \( \leq 200 \)) occurring within 24 hours after ICU admission, lasting more than 2 hours, and in the absence of other causes of pulmonary insufficiency such as cardiogenic pulmonary edema, pneumonia, pleural effusion, segmental atelectasis, pneumothorax, and pulmonary artery embolism 12. The exclusion criteria were as follows: (I) patients who died within 24 hours after surgery; (II) patients who developed severe postoperative complications such as: coma, cardiogenic shock, and gastrointestinal ischemia.” And a flowchart of patients enrollment is summarized in Figure 1.

It is a retrospective observational study and it has some limitation. Due to the limited production of NO gas and the debatable effect of iNO (see Ref14 Cochrane review 2016), there were only 43/176 patients received iNO therapy, and the iNO treatment was administered at the discretion of intensivist and the choice of patients’ surrogates. We only excluded patients with fatal complication. Fortunately, the baseline characteristics were quite matched in the two groups which made the comparison possible. We have illustrated this in limitation.

Reviewer #2: The article is very interesting. Since they are patients with longer hospitalizations than usual cardiac surgery patients, any intervention that may decrease the permanence is welcome. Other studies should be performed to see other positive effects and side effects of nitric oxide mainly in vavular patients.
Response: Thank you for the motivating comments and suggestions. Encouraged by the positive results showed in this study, a prospective RCT research has been planned.

Reviewer #3:

Dear authors

Thank you for submitting the manuscript "Effects of inhaled nitric oxide for postoperative hypoxemia in acute type A aortic dissection".

(1) Objectives of the paper and importance of the research question:

Postoperative hypoxemia in acute type A aortic dissection (AADA) is known to occur and is associated with negative outcomes. This manuscript sought to analyze the efficacy of low-dose (5-10 ppm) inhaled nitric oxide (iNO) in the management of hypoxemia following dissection repair surgery.

(1) Response:

Thank you for your comment. In this study, we found that low-dose iNO improved oxygenation in patients with hypoxemia after AADA surgery and shortened the durations of mechanical ventilation and ICU stay.

(2) Study group, methods and sample size:

Authors did not clearly describe the type of the study they conducted. It should be clearly described in the "Methods" section. The study needs to be described with regard to the "timeline" and with regard to the presence of "intervention". Following this, this study is apparently retrospective observational study. Propensity score matching was used to make the groups comparable.

Patients data were retrieved from two institutions. A proportion of 42.9% of patients had hypoxemia following dissection repair surgery. Were all the operations done in the same way? This needs to be addressed whenever the study is multicentric.

(2) Response:

We are grateful for your detailed comments and suggestions and we believe that would greatly improve our manuscript. We have revised our manuscript following STROBE guideline, "retrospective observational" was clearly added in the “Methods” section and “Title”. “timeline” and “intervention” have been clearly described in the revised manuscript.
All patients were performed by two professors, Zhongxiang Yuan and Zhiyun Xu, who are senior surgeons with over 5000 cardiac surgery experience totally, respectively. Repairment surgery for AADA was performed with the same standard surgical procedure, and the types of surgery were described in Table1. We have added this important information into article.

(3) Outcome measures:

Authors selected adequate outcome measures. When it comes to mortality, it is highly likely that the study is underpowered and sample size effect should inevitably be taken into account.

(3) Response:

Thank you for your constructive advice. Indeed, potential differences of mortality may not be showed due to the small sample size. We used PASS calculated the power for mortality, which was low in the study, however we found that low-dose iNO treatment improved pulmonary oxygenation and shortened the durations of mechanical ventilation and ICU stays among patients with hypoxemia after AADA. We have illustrated this in limitation. In fact, we have prepared a perspective RCT study to testify the benefit effect of iNO and would enroll adequate samples and would add more weight to these results.

(4) Presentation of results:

Inhaled NO ameliorated hypoxemia at 6, 24, 48, and 72 hours after initiation, and shortened the durations of ventilator support and ICU stay. There were no significant between-group differences in mortality, complications, or length of hospital stay.

As previously mentioned, this is an observational comparative non-interventional study and as such needs to follow STROBE guidelines. Authors are strongly encouraged to follow these guidelines when reporting observational trial such as this.

(4) Response:

Thank you for your valuable suggestions. We have revised our manuscript following STROBE guidelines point by point (see attachment).

(5) Discussion and interpretation:

Limitations of the study section is somewhat superficial and should go in more details. Study is underpowered to draw the conclusions based on secondary outcomes. Prospective RCT is needed. Selection of patients who had iNO remains elusive despite propensity matching.

(5) Response:
We really appreciate your advice. We have illustrated this in limitation. Encouraged by the good results showed in this study, a prospective research has been planned. If this article could be accepted, it would be very helpful for our further study.