Author’s response to reviews

Title: Transcatheter and intraoperative device closure of atrial septal defect in infants under three years of age

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Author’s response to reviews:

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled “Transcatheter and Intraoperative device closure of atrial septal defect in Infants under three years of age: Procedural Results and Long-Term Follow-Up”. These comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made corrections which we hope meet with approval. In addition, in order to improve the English editing of the article, we have sent the manuscript to a native language editing company. The responds to the reviewers’ comments are as follows:

Reviewer 1

The manuscript describe's single-center experience comparing the early and long-term results of transcatheter versus intraoperative device closure for ASDs in infants. The manuscript describes feasibility of Transcatheter and intraoperative device closures. The method's in which patients are placed into groups are not well described and thus the two groups described are not similar. The proportion of complex ASDs (multiples or rims deficiency) and the device/weight ratio in group B was significantly higher than group A as well as statistically significant differences in some demographic data and preoperative clinical characteristics. Overall the outcomes for both groups are great as well as the long-term efficacy was excellent in both groups.

Re: Thank you very much for your comments and acceptance of our article. You have reminded us of our shortcomings and we have described the method in which patients are placed into groups in more detail in the revised article. Thank you!

Reviewer 2

1- Taking into account, that the authors described in the text no residual shunts at the 6-months follow-up evaluation and considering that the Table 2 shows residual shunt of 3.4% (Group A) and 8.2% (Group B), it would be better if the immediate and short-term outcomes in the two groups should be presented separately. Additionally, for the better understanding of results it is necessary to mention the intervals of time (months) that were considered as short-term and long-term outcomes.

Re: Thank you very much for your comments. Your suggestions have inspired us a lot. Our article was not very clear about the short and long term, and the structure is not very reasonable. Our initial short-
term definition was the time from postoperative to discharge. In addition, an average follow-up of 4.5 years was inappositely defined as a long-term outcome. Therefore, referring to your suggestions, the “Procedural and Short-term Results” and “Long-Term Outcomes” parts in the original results were changed to “Intraoperative and post-operative results” and “Follow-up results” to make the description of the article more reasonable.

2- Although the successful closure rates were high, their percentages and the two failed cases presented in "Results" should also be included in "Summary".
Re: Thank you for this suggestion, we have added the two failed cases and percentages in the modified version.

3- A description of the mean (SD) and the median of follow-up in both groups as well as the minimum and the maximum period of follow-up should be included in "Results'.
Re: Thank you. Based on your comments, we have modified the description of the follow-up time in the revision. A description of the mean (SD) and the median of follow-up in both groups as well as the minimum and the maximum period of follow-up were included in “Results” in the revision.

4- I think it would be better to include in "Methods" the meaning of a "significant secundum ASD" as described by the authors in the text.
Re: Thank you very much for your comments. This is a very good suggestion. We have already revised the article, included in "Methods" the meaning of a "significant secundum ASD". We cleared the indication for ASD closure was hemodynamically significant left-to-right shunt (pulmonary to systemic flow ratio > 1.5 measured by echocardiography) manifested by enlargement of the right ventricle (RV). Your suggestion improved our article. Thank you!

5- Considering the results of this investigation, I would like to suggest including in "Conclusions", the high point of the discussion, which was the importance of the selection criteria which led the allocation of patients for the two techniques of device closure (Group A and Group B).
Re: Thank you very much for your suggestion. The allocation of patients for the two techniques of device closure (Group A and Group B) was very important. And a special strategy had been established after years of development for treating secundum ASD in infants in our center including evaluation and different procedural options. We have already revised the “conclusions” of our article, added the suggestion of allocation of patients. Considering better cosmetic effect and shorter duration of the procedure and postoperative hospital stay, transcatheter is preferred for patients with appropriate conditions. Intraoperative device closure can be performed as an alternative to percutaneous closure, particularly for infants with large, complex ASDs, young age, or low body weight.

Reviewer 3

1- The authors have to better convince the reader of the indications for intervention. By their own reports, some of these ASDs were 5mm in diameter. Why did they need to be closed?
a. I would recommend that they provide data on indications for intervention for their cohort in Table 1.
Re: Thank you very much for your comments. You have reminded us of our shortcomings, we have already revised the Table 1 and "Methods", added the indications for intervention. The indication for ASD closure was hemodynamically significant left-to-right shunt (pulmonary to systemic flow ratio > 1.5 measured by echocardiography) manifested by enlargement of the right ventricle (RV). Other indications included failure to thrive, frequent respiratory infections, increased sweating and easy fatigue, significantly elevated pulmonary arterial pressure, or strong parental request.
b. They simply state RV dilation as an indication, and Figure 1 is overly simplistic. They should provide RV dimensions indexed for BSA (Z values). These should be plotted during follow-up for each patient and individual changes documented if the authors want to claim that RV dimensions normalized, as they do now.
Re: This is a very good and professional suggestion. We know that RV dimensions indexed for BSA (Z values) is an important indicator for a more accurate assessment of the RV in infants or young children. However, up to now, the reference range of Z value proposed by scholars or guidelines is all based on
the data of white children, which is not applicable for Chinese Han infants. Currently, there is no reference range of Z value published in China. The normal reference range of echocardiographic heart index for infants and young children published by the authority in China is based on age change, although it is not very accurate, we need refer to this data. In addition, for infants and young children with atrial septal defect, the ratio of right ventricular to left ventricular end-diastolic transverse dimension (RV/LV) is a more important indicator for us to evaluate the postoperative efficacy of closure. In general it was considered a return to normal that RV/LV decreased to less than 1. We didn't go into enough detail in the original article, the results in figure1 of our article were based on the changes of RV/LV. We have made more detailed explanation in “result” and “Figure legends” in the revision. RV end-diastolic anteroposterior dimension and RV/LV were recorded before ASD closure. RV dilation was present in all patients. RV dimension and RV/LV decreased in all patients at the two-year follow-up evaluation (Fig. 1). “Enlarged RV: the ratio of right ventricular to left ventricular end-diastolic transverse dimension (RV/LV) ≥ 1; Normal RV: RV/LV < 1.” The table below is a reference to the age-based right ventricular end-diastolic anteroposterior dimension (mm) published in China for normal infants and young children.

<table>
<thead>
<tr>
<th>age</th>
<th>newborn</th>
<th>1month</th>
<th>4month</th>
<th>7month</th>
<th>1year</th>
<th>2year</th>
<th>3year</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV (mean)</td>
<td>9.3</td>
<td>9.7</td>
<td>9.5</td>
<td>10.6</td>
<td>10.8</td>
<td>11.3</td>
<td>11.6</td>
</tr>
<tr>
<td>RV(SD)</td>
<td>1.6</td>
<td>2.2</td>
<td>1.8</td>
<td>2.2</td>
<td>2.4</td>
<td>2.8</td>
<td>2</td>
</tr>
</tbody>
</table>

2- A major drawback in the study is that the authors never define how they choose the interventional approach. If this technique needs to be more widely utilized, they need to define the appropriate patient for whom this procedure is applicable. When do they choose transvenous vs. transthoracic vs. surgical closure. Guardian choice, as currently reported, does not do the indication justice.

Re: Thank you very much for your comments. We have recognized this drawback in the study and described it in detail in the revision. You know, we mentioned in “Discussion” in the original text that a special strategy had been established for treating secundum ASD in infants in our center including evaluation and different procedural options. We added how to choose the interventional approach in “Methods” in the revision. In general, the inclusion criteria for group A were as follows: secundum ASD with the presence of adequate rims (≥5 mm); the distance from the defect edge to the coronary sinus, superior and inferior vena cava, and pulmonary vein was ≥ 5mm, and that until the atrioventricular flap reached 7 mm; suitable body weight (≥10 kg) with good peripheral vascular development. The inclusion criteria for group B were as follows: inclusion criteria for group A; no specific requirement for patient weight; secundum ASD with deficient rim <1/4. Before treatment selection, all the guardians of the patients were informed of the indications, advantages and disadvantages, and specific risks of both treatments. For example, transcatheter device closure involves a short postoperative recovery time and zero incision. The intraoperative device closure requires minimal incision but no vascular injury and X-ray exposure and can be immediately converted to surgical repair in the operating room. Generally percutaneous closure is preferred for patients who satisfied the inclusion criteria for group A, whereas the final treatment plan must be considered along with the preferences of the patient’s guardian.

3- The authors underplay the morbidity in their study.

a. 20% morbidity is high unless they can clarify why they believe their complications are less serious.

Re: Thank you very much for your comments. Postoperative complications are described and discussed in more detail in the revision. A high overall incidence of perioperative complications (20.4%) was
observed in the two groups, but most of them were minor complications including transient cardiac arrhythmias, hematoma at the access site, pericardial effusion, hydrothorax, or pneumonia that could be well managed without leaving sequelae. In addition, death, erosion, tamponade, cardiac perforation, atrioventricular valve distortion, endocarditis, thromboembolism, or permanent rhythm disturbances were absent in both groups.

b. It is not clear based on their description how they evacuate air and fluid from the right chest in the trans-thoracic group prior to completion of the procedure. Given the 5 morbidity events, the authors should elaborate on what their practices are and how the complication was managed in these 5 patients.

Re: Thank you very much for your suggestion. We have already revised the article, added the description how we evacuate air and fluid from the right chest in the trans-thoracic group in “procedure” and added subsequent management for 5 morbidity events in “Discussion”. Before the incision was closed, the aspirator was used to completely remove the fluid in the right chest cavity and pericardium and empty the air by expanding the lungs. For the 5 morbidity events, based on our experienced, only a periodic review was needed for a small amount of hydrothorax or pericardial effusion after procedure. The effusion can be absorbed and eliminated within one month. For values higher than the moderate volume of effusion, ultrasonic positioning puncture and catheter drainage were generally required.

4. The discussion is wordy and can be significantly shortened. Also, 4-year follow-up does not qualify as long-term follow-up and this should be changed throughout the manuscript.

Re: Thanks very much for taking your time to review our manuscript. Your comments have given us important tips. We have cut out some of the discussion and made the language more concise. An average follow-up of 4.5 years was inappropriately defined as a long-term outcome. Therefore, referring to your suggestions, we have revised this description throughout the manuscript. And the “Procedural and Short-term Results” and “Long-Term Outcomes” parts in the original results were changed to “Intraoperative and post-operative results” and “Follow-up results” to make the description of the article more reasonable. Thank you very much!