Peer Review File

Article information: http://dx.doi.org/10.21037/tp-20-202.

Reviewer Comments

The authors present feasibility of simultaneous transthoracic interventions for multiple cardiac defects, namely ASD, VSD, pulmonary stenosis and PDA in a series of 20 children. Short-term outcomes were good and without major complications.

Major comment:

1. The value of the data are unfortunately extremely limited, as there is no comparison group of children with the same combinations of heart defects that have been treated with open heart surgery (according to the authors, only 15% received the intervention, so where and how are the results of the other 85% of infants?). A comparison in terms of perioperative management and outcome (including some statistical analyses) would be of great value to adequately assess the novel intervention.

Reply 1: Thank you very much for the suggestion. Between March 2015 and December 2019, 133 patients were admitted to our center with multiple CHD and were allocated to groups on the basis of the surgical method selected by the patient. A group consisted of 20 patients who underwent an attempt of simultaneous transthoracic intervention were referred to this study. These numbered 15 males and 5 females, with a mean age of 18.8 ± 8.6 (range, 4–36) months and a mean weight of 8.3±2.5 (range, 4.8–12.5) kg. Other 113 patients who refused device closure received conventional surgical repair with cardiopulmonary bypass (CPB).

In this study, 20 cases were occluded successfully without any thoracotomy conversion. The anesthesia time and operation time were 130–200 (mean, 158 ± 22) minutes and 56–120 (mean, 75 ± 13) minutes respectively. The amount of

intraoperative blood loss was 0.7–6.9 (mean, 3.3 ± 1.9) ml/kg. The length of postoperative ventilation ranged from 0.3 to 4 (mean, 2.2 ± 1.3) hours with postoperative hospital stay ranging from 2 to 8 (mean, 5.5 ± 1.6) days.

Other 113 patients with multiple congenital cardiac defects were corrected by cardiac surgery. The anesthesia time and operation time were 150–360 (mean, 227 ± 47) minutes and 90–300 (mean, 181 ± 43) minutes respectively. The amount of intraoperative blood loss was 2.2–27.3 (mean, 10.1 ± 4.1) ml/kg. The length of postoperative ventilation ranged from 0.5 to 10 (mean, 3.3 ± 2.3) hours with postoperative hospital stay ranging from 3 to 13 (mean, 6.8 ± 2.4) days. Both time of anesthesia and time of surgery, length of postoperative ventilation and length of postoperative hospital stay were significantly shorter in the intervention group compared with the CPB group ($p < 0.05$).

As suggested, we have added some data (see Page 6, line 86-88, 98-99 & Page 9, line 137-138 & Page 9-10, line 161-165). And a comparison in terms of perioperative management and outcome has been presented in Table 2 (see Page 20, line 315-318).

Minor comments:

1. The introduction should focus more on current application and challenges of the used technique and describe, what new information the case series will add to the reader. Is this intervention really as new as the authors claim?

Reply 1: Thank you very much for the suggestion. Recent advances in diagnosis, surgery and interventional management have significantly changed the quality of life of patients with congenital heart disease. However, traditional open-heart surgery with CPB has been criticized because of operative trauma, an unsightly scar, and CPB-associated complications. Catheter-based closure is limited for infants because of small vascular diameters, and radiation exposure is still a disturbing problem for children. Transthoracic intervention for multiple cardiac defects, as a new technology that obviates the need for surgery or a multistaged interventional procedure with

prolonged fluoroscopy time, has been reported in only a few studies.

Therefore, we present our experience with simultaneous transthoracic interventions for multiple cardiac defects in a series of pediatric patients. Our study indicated that the procedure is technically feasible, with excellent short-term outcomes. For different lesions, the appropriate surgical incision can render the intervention minimally invasive and safer. And PS→VSD→PDA→ASD may be the most widely acceptable operational sequence.

We have modified the Introduction of our text as advised (see Page 5, line 66-70& 72-74& 77-79).

2. Methods should describe more the periprocedural monitoring: Which antibiotic was given periprocedural? What is the definition of "serious arrhythmia", which did not occur? Which types of arrhythmia occurred and how were they treated? With which examinations were arterial thromboses (cranial?) excluded? Is there a neurodevelopmental follow-up of the infants?

Reply 2: Thank you very much for the suggestion. All patients with device implantation received antibiotics during the operative procedure (cefuroxime sodium, 30 mg/kg) and the following day (cefuroxime sodium, 100 $mg•kg^{-1}•d^{-1}$, q8h). We have described antibiotic monitoring in the Procedures (see Page 8, line 125-127).

In this study, there was no arrhythmia observed in 20 patients during hospitalization and the post-operation period. Based on our experience with transthoracic intervention for isolated CHD, complete atrioventricular block occurred, defined as "serious arrhythmia", needed to be converted to conventional open-heart surgery. Temporary arrhythmia that occurs in most cases did not require therapy and underwent spontaneous recovery. We have modified our text as advised in the Procedures (see Page 7, line 122) and the Results (see Page 10, line 168-171).

Perioperative physical examination of the nervous system is very important in the diagnosis of cranial arterial thromboses. Computed tomography should be combined when necessary. All cases were occluded successfully with any complications during hospitalization and the post-operation period, showed good growth and development, including neurodevelopmental. As suggested, we have described more about the periprocedural monitoring in the Procedures (see Page 8, line 129) and the Results (see Page 10, line 166-167).

3. To be able to better assess the interventions, following data should be added to Table 1 (Patients characteristics): Body weight at intervention, co-morbidities, previous (failed?) interventions, previous drug therapy.

Reply 3: As suggested, we have added the following data to Table 1 (Patients characteristics): Body weight at intervention, co-morbidities, previous interventions, previous drug therapy (see Page 18).

4. To make it easier for the reader, the CHD diagnoses and the corresponding interventions (including information on used devices) should be listed in a table or figure. Blood loss should be presented as ml per kg of body weight. Both time of anesthesia and time of surgery should be presented. Length of postoperative ventilation and length of hospital stay should also be added in order to be able to better classify the procedure.

Reply 4: Thank you very much for the suggestion. We have added Figure 3 to show the CHD diagnoses and the corresponding interventions as advised (see Page 21, line 323-325). Blood loss has been presented as ml per kg of body weight in the text (see Page 9, line 147-148). And, both time of anesthesia and time of surgery, length of postoperative ventilation and length of postoperative hospital stay had been added in Results as suggested (see Page 9, line 145-150).

5. Although the devices can be clearly seen, the image quality of Figure 2 (X-ray) should be improved.

Reply 5: As suggested, we have uploaded Figure 2 with higher image quality.

6. Figure 4A (inferior sternum incision) should be referred to in the manuscript text.
Reply 6: Thank you very much for the suggestion. In this study, a 1.5–2.0-cm inferior sternum incision (Figure. 4A) was made in 11 patients as mentioned in Results. Normally, the free wall of the RV is exposed via a minor inferior sternum incision for the closure of a perimembranous VSD, with a shorter distance and directional performance can vertically advance the delivery sheath across the VSD. We have described more of inferior sternum incision in the Results and Discussion as advised (see Page 9, line 157-160 & Page 11, line 196-200).

7. Discussion on periprocedural hemodynamics of PS and VSD closure is too short and should be extended by more references. Figure 3, only referred to in the Discussion, should be relabeled Figure 4 (last Figure). Discussion on advantages and disadvantages of this new technique is too short and does not sufficiently highlight the current use of the technique (should include more up to date literature).
Reply 7: Thank you very much for the suggestion. In pulmonary valvuloplasty or defect closure, the question remains as to which should be performed first. In theory, correcting the defects first will diminish the shunt volume subsequently reducing the gradient across the pulmonic valve. And, there was a fear of acute congestive heart failure and pulmonary edema as a result of increased pulmonary blood flow into previously protected pulmonary artery circulation. However, when both PS and defects coexist, left-to-right shunting is prevented if right ventricular pressures suddenly increase owing to the outflow obstruction caused by the pulmonary valvuloplasty. Moreover, from a technical view, performing a balloon valvuloplasty prior to deployment of an occluder device would limit the possibility of potentially dislodging the device. We have discussion more on periprocedural hemodynamics of PS and defects closure by references in the Discussion as advised (see Page 12, line 221-224).

Besides, we have relabeled Figure 3 as Figure 5 (last Figure) (see Page 21, line 328-332).

Transthoracic intervention, a hybrid technique has been widely used in the past decades, associated with no age or weight limitation, shorter distance and directional performance, decreased surgical morbidity, shorter duration of hospital stay, and avoidance of radiation exposure and issues with satisfactory vascular access. Moreover, with the real-time echocardiography monitor, the operative process can better observed and guided. Once the device fails or procedure unsuccessful, it can be easily converted to conventional surgery with CPB. Of course, the new technology still has its limitations. It must be performed under general anesthesia with tracheal intubation. And its minimally invasion has been questioned. As suggested, we have added discussion on advantages and disadvantages of this new technique include more up to date literature in the Discussion (see Page 10-11, line 177-186).

8. Statistics: The presentation of variables and results in mean, range, average is incorrect (mean cannot be a range, presentation of average /SD?).
Reply 8: Thank you very much for the suggestion. We have corrected the presentation of variables and results in mean, range, average (see Page 3, line 45、55 & Page 8-9, line 143-145 & Page 9, line 151-152 & Page 10, line 166 & Page 18-19).

9. The authors should get advice by an English medical language expert for further language improvements.
Reply 9: We had done the Language Editing and got the certification.