Transcatheter device closure of ventricular septal defects in children: a retrospective study at a single cardiac center

Saad Q. Khoshhal, a Mansour B. Al-Mutairi, b Abdulhameed A. Alnajjar, b Mohamed M. Morsy, b,c Sherif S. Salem, b,d Mustafa Al-Muhaya, b Khaled M. El-Harbii, a Hany M. Abo-Hadded a

From the aDepartment of Pediatrics, Faculty of Medicine, Taibah University, Madinah, Saudi Arabia; bDepartment of Pediatrics, Madinah Cardiac Center, Madinah, Saudi Arabia; cDepartment of Pediatrics, Faculty of Medicine, Sohag University, Sohag, Egypt; dDepartment of Pediatrics, Faculty of Medicine, Menoufiya University, Menoufiya, Egypt; eDepartment of Pediatrics, Faculty of Medicine, Mansoura University, Mansoura, Egypt

BACKGROUND: Ventricular septal defect (VSD) is the most common congenital heart disease in the pediatric population. Nowadays, transcatheter closure is considered a feasible method of therapy for most muscular and some perimembranous types of VSDs.

OBJECTIVES: Assess the safety, efficacy and outcome of percutaneous transcatheter closure of VSDs in children.

DESIGN: Retrospective, single center study.

SETTING: Madinah Cardiac Center, Madinah, Saudi Arabia.

PATIENTS AND METHODS: The study included all consecutive children who underwent transcatheter closure of isolated VSD during the period from December 2014 to January 2019. The data were collected from hospital database medical records. Transthoracic echocardiography (TTE) and an electrocardiogram (ECG) were done before and after the procedure in all the patients. The device was implanted by the retrograde or antegrade approach. All patients were subjected to follow-up evaluation at 1, 3, 6, 12 months, and annually thereafter with TTE and ECG.

MAIN OUTCOME MEASURES: Procedure success rate, clinical follow-up, TTE.

SAMPLE SIZE: 70 children.

RESULTS: The mean (standard deviation) age of patients was 10.2 (4.1) years (range: 2-18 years), and their mean body weight was 30.9 (13.9) kg (range: 7.0-57.7 kg). Forty-eight (68.6%) children had muscular VSD (mVSD), and 22 (31.4%) children had perimembranous VSD (pmVSD). The majority of defects were closed via the retrograde approach using the Amplatzer muscular occluder device. At 24 hours after the procedure, the success rate was 90%. Only four (5.7%) cases had major adverse events including complete atrioventricular block, hemolysis, and thrombus formation.

CONCLUSIONS: Transcatheter closure is a safe and feasible procedure in VSDs of various morphologies, with a low adverse event rate.

LIMITATIONS: Retrospective design, single-center study, absence of control group.

CONFLICT OF INTEREST: None.
Ventricular septal defect (VSD) is currently the most common congenital heart disease found in the pediatric population, representing 20% of isolated congenital heart diseases.1 Despite the fact that VSDs can present in any part of the interventricular septum, the most common morphological variants are perimembranous VSD (pmVSD) and muscular VSD (mVSD) (anterior, mid, posterior, inlet, or outlet in location); the supracristal type is less common.2 Depending on the size and flow of the VSD, hemodynamic compromise may occur. Closure is mandatory in hemodynamically unstable patients.3

Traditionally, VSDs have been closed with an open surgical approach, but there remains a risk of complete atrioventricular block (CAVB), infection, postpericardiotomy syndrome, chylothorax, and complications of cardiopulmonary bypass (e.g., myocardial and pulmonary injury, electrolyte disturbance, coagulopathy, and acute kidney failure). In addition, longer intensive care unit (ICU)/hospital stays postoperatively occur as compared to nonsurgical interventions.15 Catheter-based interventions are showing promising results compared to surgery since the first reported case in 1988 with acceptable results.6,7

This study aims to assess the safety, efficacy, and outcome of transcatheter closure of different anatomical variants of VSD in children in a major cardiac center in Saudi Arabia. This included all the small and most of the moderate muscular VSD types (outlet, mid-muscular, apical; posterior and anterior variants), and included most of the pmVSD type, especially with aneurysmal tissue.

PATIENTS AND METHODS
This retrospective study was conducted at the Madinah Cardiac Center between December 2014 and January 2019. The data for all consecutive children who underwent transcatheter VSD closure during the study period were retrieved and included in the study. A complete pre-procedural evaluation included clinical examination, chest X-rays, electrocardiograms (ECG), trans-thoracic echocardiogram (TTE) and specific laboratory investigations to rule out any bleeding disorders (e.g., complete blood count, platelet count, prothrombin time, and activated partial thromboplastin time).

Transcatheter VSD closure was indicated in the following conditions: (1) significant left-to-right shunt affecting the child clinically; e.g. failure to thrive, and/or recurrent chest infections in spite of adequate medications (≥ 2 attacks of chest infections per month that necessitate medical management). (2) Chest x-ray showing cardiomegaly and/or lung plethora. (3) TTE evidence of significant shunt (increased left atrial and left ventricular end diastolic diameters above upper normal limits according to the child body weight). Also, (4) The estimated pulmonary artery blood pressure less than 2/3 of the systolic blood pressure (measured as the gradient over tricuspid valve regurgitation plus right atrial pressure in relation to the systemic pressure at the same time). (5) Specifically in pmVSD type, it was mandatory to have a good aneurysmal tissue (for better deployment of the occluding device inside it away from aortic valve) and a sub-aortic rim ≥ 4 mm (to avoid compression of the device on the aortic valve and other adjacent structures).

Patients were excluded from the procedure if: (1) age was less than 2 years, and the body weight less than 8 kg, (2) the size of the VSD was larger than 2/3 of the aortic annulus, (3) for the mVSD type, the presence of significant aortic valve prolapse, aortic regurgitation, or inadequate aneurysmal tissue. Also, patients with any additional lesions requiring surgical intervention were excluded.

Procedure
The procedure was done under general anesthesia with transesophageal echocardiography (TEE) and fluoroscopic guidance. Access was via the femoral artery and femoral vein. A 100 U/kg heparin dose and intravenous antibiotics were given to all patients prior to the procedure. A hemodynamic study was performed confirming the TTE findings (2-D imaging and color flow in short- and long-axis views). The VSD was profiled through angiographic evaluation of the left ventricle (LV) at a 60° left anterior oblique / 20°cranial projection. At the maximum diastolic phase, the angiography delineated the VSD location, size of VSD (at the narrowest area), and number of defects and their relationship with the surrounding structures. The majority of VSDs were closed by the retrograde approach via the femoral artery, in which the VSD is crossed from the LV side with a Judkins right coronary catheter (Infinity, CORDIS) and Terumo guidewire (Radifocus, Terumo Corporation) combination, and then the tip of the JR catheter was placed in the right ventricle (RV). The appropriate device is delivered, where the distal RV right ventricular disc was initially deployed, followed by the waist and the LV disc.

In some cases, after crossing the VSD from the left to the right ventricle using a guide catheter, the Terumo guidewire was inserted into any pulmonary artery branch and then snared out from the venous end, making an arteriovenous loop. The delivery sheath was advanced antegrade over the wire from the venous side. The tip of the delivery sheath was then crossed to the RV right ventricular side. The delivery sheath was then followed by the waist and then the LV disc.
into the LV apex. From that point, the device was conveyed through the delivery sheath under fluoroscopic guidance.

The type and size of the device was selected during the procedure based on VSD type and its narrowest diameter. In the majority of cases (64 cases), we used the Amplatzer muscular VSD Occluder (AmVSDo) device (AGA medical Corporation, Plymouth, MN, USA), but in few of cases (6 cases) especially with a thick interventricular septum, we used Amplatzer Duct Occluder type-I (ADO-I) device (AGA medical Corporation, Plymouth, MN, USA). The size of the device was either equal to or up to 2 mm larger than the angiographically measured narrowest defect size. For the pmVSD type, we selected pmVSDs with subaortic rim ≥4 mm because the length of the left retention skirt of the device is 4 mm larger than the waist diameter and the right retention skirt is 3 mm larger, so the device can be successfully implanted without creation of aortic regurgitation or rhythm disturbances. Post-deployment, LV and ascending aortic root angiograms were repeated to confirm the final position of the device, to assess any residual shunt, and to confirm the presence or absence of aortic insufficiency. Procedure success was defined as successful closure of the VSD with the device with appropriate placement without any residual or with mild residual shunt (color doppler flow jet ranging 1-2 mm width).

The color of the urine was observed for 24 hours after the procedure to exclude hemolysis. Oral aspirin (5 mg/kg/d) was prescribed for 6 months to decrease the risk of thromboembolism. In addition, infective endocarditis prophylaxis was taken into consideration following the procedure. All patients underwent chest x-ray, ECG and TTE before hospital discharge and then followed up at 1, 3, 6, 12 months after the procedure, and yearly thereafter.

Statistical analysis

Data were analyzed using IBM SPSS software package, version 20.0 (IBM Corp., Armonk, NY, USA). Data were expressed as the mean (standard deviation) for continuous variables and as frequency or percentage for nominal variables.

RESULTS

Data on 70 children (28 males and 42 females; \( P = .0276 \)) were collected retrospectively from hospital database medical records (Table 1). The VSD variants included 22 children diagnosed to have pmVSD type (partially covered with aneurysmal tissue of tricuspid valve); and 26 patient with outlet mVSD (22 with low outlet, and 4 with high outlet subtypes), 18 patient with mid mVSD (12 anterior, and 6 posterior subtypes), and 4 apical mVSD. The mean size of the defects by TTE was 5.77 (1.89) mm (range: 3 - 11.5 mm) (Table 2). The mean procedure time was 115.8 (27.0) minutes (range: 92-138 minutes), and the mean fluoroscopy time was 21.92 (4.5) minutes (range: 17.5-27 minutes) (Table 3). Other procedure data as the mean PA pressures (mmHg), Qp/Qs, VSD narrowest diameter on TEE and on left ventricular (LV) angiography, the diameter of device used, its type, and route of deployment are listed in Table 3. No significant difference was observed in the size of the defect measured either by TTE, TEE or measured by LV angiography (\( P = .059 \)). Immediately after VSD closure, the procedure was successful (presence of mild residual shunt 1-2 mm or no residual shunt) was observed in 59 of 70 (84.3%) patients. By 24 hours after discharge, the procedure was successful in 63 (90%) patients. By 3 months, success increased to 65 (92.8%) and by 1-year follow up, success was achieved in 67 (95.7%) patients.

The adverse events (minor and major) reported in patients who underwent attempted VSD device closure are listed in Table 4 compared with data from other sources. A minor complication was defined as an event that may require drug therapy but was not life threatening, with no long-term sequelae, and which did not require long-term therapy. On the other hand, a major complication was defined as an event that resulted in death, potentially life-threatening events, long-term sequelae (>6 months), and need for surgery. All patients in the study survived without any peripheral vascular injury, or severe adverse events (death, valve injury requiring surgical treatment, infective endocarditis, device embolization, cardiac perforations) during the early period or follow-up.

Residual shunting (<2 mm) immediately after the procedure was detected in 11 (15.7%) patients, which decreased significantly during the follow-up evaluation of patients. Transient cardiac conduction abnormalities were seen in 2.9% of patients during device deployment, which disappeared shortly. Other than this, there was no new onset rhythm disturbance during 1-year follow-up. Four cases with major adverse events (5.7%) were reported in our study. The procedure was aborted in one patient aged 3 years, in which the defect was the subaortic pmVSD type. After partial release of the AmVSDo device into the defect, the patient developed cAVB with no response to steroids (methylprednisolone IV, 1 mg/kg/dose), leading to hemodynamic instability (severe bradycardia and hypotension). The sinus rhythm was restored only when the device coils were pulled back into the sheath again. Therefore, the procedure had to be stopped without deployment of the device.
Then, the defect was closed surgically 6 months later. A 4-year-old child with high outlet mVSD developed persistent cAVB after the procedure, and the child was sent to surgery to remove the device (AmVSDo) and close the defect. A third patient developed persistent gross hematuria and hemolytic anemia requiring blood transfusion following the ADO-I device implantation, which was tackled with device removal surgically and defect closure. In the day following the procedure, a fourth patient having the pmVSD type showed a small echogenic mass by TTE in the LV outlet track (LVOT) just below the aortic valve and attached to the VSD device (AmVSDo), mostly a thrombus or a blood clot, so the patient was started on heparin infusion for 7 days. The follow-up echo showed complete dissolution of the mass and the patient was discharged. During the procedure of a child with pmVSD; the right ventricular disk of the Amplatzer device was released within the right atrium, catching the septal leaflet of the tricuspid valve, and causing severe tricuspid valve regurgitation. After assessment by TEE, the disc was repositioned by inflation of a balloon inside the right atrium, thus ending the severe valvular regurgitation. There was no statistical correlation between the type of the device used for closure, or the route of device deployment with the rate of complications (data not shown).

**DISCUSSION**

Nowadays, percutaneous trascatheter closure is considered feasible therapy for VSD compared to closure by surgery, which carries the risks of complete atrio-
ventricular block (cAVB) (about 2.9-5.7%), and cardio
pulmonary bypass complications and wound infection,
with higher morbidity and mortality rates.8-10 According
to the American College of Cardiology/American Heart
Association guidelines, VSD closure should not be done
in patients with severe pulmonary artery hypertension;
with pulmonary systolic pressure greater than two thirds
systemic, and a net right-to-left shunt.11 This was con-
sidered in the this study during inclusion of the partici-
pating children performing the VSD closure procedure.

Various types of VSDs can be closed percutane-
ously; in this study, 68.6% of the included children had
mVSD and 31.4% diagnosed by pmVSD. The common-
ly used devices in literature are the Amplatzer family of
occluders designed either for closure of different types
of VSDs or for other indications.3 The majority of cases
(91.4%) were closed by the AmVSDo device. The wide
use this device in different variants of VSD in literature
provide exceptionally good results with minimal comor-
bidities and is correlated with good outcomes, which is
consistent with our results.12-13 The choice of AmVSDo
device (with a 7-mm long connecting waist) for clos-
ing the pmVSDs was well considered. The close prox-
imity of the pmVSD to the aortic and tricuspid valves
as well as the conduction system, which passes at the
posterior border of these defects, makes closure a chal-
lenge. Specially designed eccentric Amplatzer devices
for closing pmVSD did not work perfectly in reports of
its use. It also could produce potential complications
resulting from compression on adjacent structures, such
as rhythm disturbances or valve incompetence.14

After 24 hours, the success rate was 90%. This was
comparable to many previous studies that showed
good results for this procedure with a success rate rang-
ing from 90–97%.15-18 Approximately, 5-6.7% of patients
who undergo VSD closure will develop a trivial residual
shunt,6 but a significant reduction of residual shunt
occurs during the first year follow-up after the proce-
dure.19 This could be due to closure of the tiny residual
leaks by endothelialization of the device.20

Table 4. Adverse events of the procedure in Madinah Cardiac Center compared with data from other sources.

| Minor adverse events                        | MCC Experience (n=70) | European VSD Registry (n=430) | Rajaie Cardiac, and Medical Center, Iran (n=110) | Mehta Institute of Cardiology and Research, India (n=376) |
|--------------------------------------------|----------------------|-------------------------------|-----------------------------------|--------------------------|
| Residual shunt (>2mm) immediately after the procedure | 11 (15.7)            | 65 (15.1)                     | 7 (6.4)                          | 7 (1.9)                  |
| Transient cardiac conduction abnormalities (bradycardia/asystole/cAVB) | 2 (2.9)              | 4 (0.9)                       | 9 (8.2)                          | 2 (0.5)                  |
| Hematoma of the groin                       | 1 (1.4)              | 3 (0.7)                       | 0                               | 5 (1.3)                  |
| Others (fever >38°C, temporary loss of peripheral pulsations) | 2 (2.9)              | 5 (1.2)                       | 10 (9)                           | 32 (8.5)                 |

| Major adverse events                        | MCC Experience (n=70) | European VSD Registry (n=430) | Rajaie Cardiac, and Medical Center, Iran (n=110) | Mehta Institute of Cardiology and Research, India (n=376) |
|--------------------------------------------|----------------------|-------------------------------|-----------------------------------|--------------------------|
| cAVB (permanent) that required surgery/pacemaker | 2 (2.9)              | 8 (1.8)                       | 2 (1.8)                           | 1 (0.3)                  |
| Hemolysis requiring surgical removal of device | 1 (1.4)              | 5 (1.2)                       | 0                               | 1 (0.3)                  |
| Thrombus or clot formation at device site   | 1 (1.4)              | 0                             | 0                               | 0                        |
| Device embolization                         | 0                    | 4 (0.9)                       | 1 (0.9)                          | 1 (0.3)                  |
| Infective endocarditis                      | 0                    | 2 (0.5)                       | 0                               | 0                        |
| New-onset valvular regurge requiring surgery | 0                    | 0                             | 1 (0.9)                          | 1 (0.3)                  |
| Death                                       | 0                    | 1 (0.2)                       | 0                               | 0                        |

Data are number (%). cAVB: Complete atrioventricular block.
Some concerns remain over the percutaneous transcatheter technique because of the high exposure to radiation, especially for infants and children; and the increased potential risks of vascular complications caused by puncture of the femoral artery for angiography. Fortunately, the occurrence of these factors were consistent with other studies, and these risk factors did not appear to have any adverse impact on the participating children in our study.\textsuperscript{21-24}

Blood transfusion and hemolysis are other adverse events that may happen soon after device implantation (1% of cases). Hemolysis may occur because of mechanical injury to red blood cells with significant residual shunts following device closure. It can be minimal and self-limited or it may be severely needing surgical removal of the device.\textsuperscript{16,17} However, in our study, there was only one case reported with hemolysis that needed blood transfusion, and surgical removal of the device and defect closure.

The commonest major reported complication of VSD closure is arrhythmia (risk 4.6-17% following device implantation).\textsuperscript{25} In our study, transient cardiac conduction abnormalities represented 2.9% of the whole cases, which was treated with intraoperative steroids. Recent studies have assumed that cAVB is the most significant arrhythmia leading to complications either immediately during the procedure or during the follow-up period, with an incidence ranging from 3.5% to 8.6%,\textsuperscript{19} but we only reported two children in this study (2.8%) with cAVB. An oversized device, low body weight, younger age, and repeated maneuvers are the potential risks for the development different types of arrhythmias.\textsuperscript{26,27} This can be explained by myocardial edema due to an immature myocardium with higher water content and tender structure in young patients leading to a higher incidence of cAVB in younger patients.\textsuperscript{28}

The association of cAVB with the pmVSD type is a common finding in the literature, with an incidence rate varying from 2% to 7.5%.\textsuperscript{7,17,18} This adverse event may be explained by the proximity of the conduction system of the heart with the rim of the pmVSD, so the risk for developing cAVB increases whether the approach is via transcatheater or surgical.\textsuperscript{27,28} One of our children diagnosed with cAVB had pmVSD, but the other one had high outlet mVSD, and both needed surgical intervention for closing the VSDs.

According to reports from the European Registry and the opinion of Dr. Kurt Amplatz, the designer of the muscular VSD occluder device (oral report), the cutting of the tricuspid tendinous chords causing regurgitation during the device implantation is possible in practice, especially for defects located in the inlet area of the muscular septum.\textsuperscript{6,14,29} In addition, new aortic regurgitation following VSD device closure was reported to be approximately 3.4%.\textsuperscript{25} Favorably, this study did not report any new-onset valvular regurgitation require treatment.

There were certain limitations in this study. First, as a retrospective study, the data is recorded only from the hospital database and any missing data is irretrievable. Second, as a single-center study, the results are not generalizable. In addition, there was no control group (i.e. a group did VSD surgical closure) to compare with our findings.

In conclusion, this study confirmed the outstanding safety and efficacy benefits of transcatheter VSD closure in children and showed a minimal complication rate. These results can be fulfilled with proper case selection during inclusion of patients and with a team that has good expertise.

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Disclosure of Benefit
Authors have no conflict of interests and the work was not supported or funded by any commercial party related directly or indirectly to the subject of this article.

Ethical approval
Ethical Committee Board of Madinah Cardiac Center, (Reference no. MCC2018-18), Madinah, Saudi Arabia.

Consent
After explaining the benefits and the risks of the procedure, a detailed and informed written consent was taken from all the eligible patients or parents before the procedure.
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