Atrial septal defect (ASD) is a hole in the interatrial septum (IAS) of the heart that is one of the most common congenital heart diseases (CHD). Percutaneous transcatheter device occlusion is one of the techniques that have been developed for the closure of atrial septal defects. The primary objective of this study is to assess the safety and efficacy of septal occluder devices in the management of atrial septal defect in children. We searched PubMed, Science Direct, and Google Scholar databases to collect relevant articles according to a predetermined eligibility criteria and included 23 papers of different study designs in this systematic review. We found that transcatheter closure is safe and effective in most children with ASD. The major complications reported could be avoided by comprehensive clinical assessment and echocardiographic evaluation to determine appropriate device size and implantation strategy per individual child. Further research involving more clinical trials with larger sample size and longer duration of followup is required to improve the safety of existing devices for their use in all children with ASD despite their weight and defect size, and also the efficacy of newer devices such as biodegradable septal occluders.

Abstract

Atrial septal defect (ASD) is a hole in the interatrial septum (IAS) of the heart that is one of the most common congenital heart diseases (CHD). Percutaneous transcatheter device occlusion is one of the techniques that have been developed for the closure of atrial septal defects. The primary objective of this study is to assess the safety and efficacy of septal occluder devices in the management of atrial septal defect in children. We searched PubMed, Science Direct, and Google Scholar databases to collect relevant articles according to a predetermined eligibility criteria and included 23 papers of different study designs in this systematic review. We found that transcatheter closure is safe and effective in most children with ASD. The major complications reported could be avoided by comprehensive clinical assessment and echocardiographic evaluation to determine appropriate device size and implantation strategy per individual child. Further research involving more clinical trials with larger sample size and longer duration of followup is required to improve the safety of existing devices for their use in all children with ASD despite their weight and defect size, and also the efficacy of newer devices such as biodegradable septal occluders.

Introduction And Background

Every year, about one to two out of 1,000 live babies are diagnosed with atrial septal defect (1), which is the second most common congenital heart disease (CHD). Atrial septal defects (ASD) make up 10%-15% of all congenital heart diseases (1).

During the fourth week of gestation, atrial septa grow caudally as the septum primum and septum secundum from the roof of the atria, dividing them into the right and left atria (2). The two atria communicate during fetal life through a space between the septum primum and septum secundum called the foramen ovale (3). The two septa normally fuse as a single septum soon after birth, serving as a barrier between the right and left atria (2). A hole in this septum is known as an atrial septal defect. There are four types of atrial septal defects depending on the location: ostium secundum defect, ostium primum defect, sinus venous defect (further classified as superior and inferior), and coronary sinus defect (2). Among them, ostium secundum defect is the most common (2).

Atrial septal defect serves as a window between the two atria that should not exist after birth. It is usually an asymptomatic congenital heart disease, with a shift of blood flow from the left atrium to the right atrium as shown in Figure (2). Patients are usually asymptomatic and often undiagnosed till adulthood (2). Large defects can present with exercise intolerance, syncope, pulmonary hypertension, increased incidence of pneumothorax, and increased mortality (2). There is also a possibility of severing of the shunt with blood flowing from the right atrium to the left atrium, known as Eisenmenger Syndrome, when right atrial pressures exceed that of the left, leading to cyanosis, dyspnea on exertion, increased pulmonary vascular resistance and increased susceptibility to infection (5). Another serious potential complication of atrial septal defect is transient ischemic attack/stroke (3).
Spontaneous closure of ASD in the first year of life commonly occurs in patients with ASD smaller than 5mm [2]. Defects larger than 1 cm usually require medical or surgical closure [2]. Previously, surgical closure was the standard of care for ASD, but over the last 40+ years, transcatheter devices have rapidly emerged as the routine in children [3,4]. As of today, the devices currently available for ASD closure include the Amplatzer Septal Occluder, Occlutech Figulla Flex II, Gore Cardioform Septal Occluder, Cardioseal, Nit Occluder ASD-R, CardioFix Septal Occluder, Ultracept II ASD Occluder, and Carag Biosorbable Septal Occluder [5].

In transcatheter device closure of ASD, a catheter enclosing the septal occluder device is inserted through a vein in the groin (right femoral vein) under echocardiographic (transesophageal echocardiography/TEE) and/or fluoroscopic guidance and traversed upwards through the inferior vena cava (IVC) to the atrial septal defect as illustrated in Figure 1 [6,7]. The occluder device within the catheter exists folded up as an umbrella, and is pushed through the catheter to plug the defect in the atrial septum, after which the catheter is removed [4]. Eventually, cardiac tissue grows over the device (endothelialization), further securing it in place [6]. Unlike surgical closure of ASD, transcatheter device closure has a short post-operative recovery time, and requires no incision [8].

Prior to device closure of ASD, patients must be assessed for hemodynamics (in patients with right-to-left shunt), morphologic characteristics of the defect (size and presence of sufficient rim), presence of multiple defects, and presence of other cardiac conditions/abnormalities [5,9]. Large defects may lead to prolapse of the left atrial disk of the device into the right atrium [3]. Large defects with rim deficiencies may lead to further complications such as device embolization, impingement of nearby cardiac structures, and erosion [9]. Transcatheter device closure of ASD is indicated in children with acceptable hemodynamics with suitable anatomical features, transient right to left shunt with history of paradoxical emboli, right to left shunt with symptomatic cyanoses who do not require the communications to maintain cardiac output, and small ASDs with suspected high risk of thromboembolic events [9]. It is not indicated in patients with ASD other than septum secundum defect, small septum secundum defects without hemodynamically significant shunt and other risk factors, and in patients with advanced pulmonary vascular obstructive disease [9].

This systematic review aims to assess the safety and efficacy of septal occluder devices in the management of atrial septal defect in children. Patent foramen ovale (and other congenital heart diseases) were not included in this study.

Review Methods

Study Protocol

We created a systematic review in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) 2020 Guidelines [11].

Sources of Data Collection and Search Strategy

We reviewed scientific literature from three databases, PubMed, Science Direct, and Google Scholar, using keywords with Boolean words and medical subject heading (MeSH) from the last five years (2017–2022). Our search strategy is detailed in Table 1.
TABLE 1: Search Strategy

| DATABASE | SEARCH | RESULTS |
|----------|--------|---------|
| PubMed   | "Heart Septal Defects, Atrial" OR "Heart Septal Defects, Atrial/complications" OR "Heart Septal Defects, Atrial/surgery" OR "Heart Septal Defects, Atrial/therapy" [Mesh] OR "Heart Septal Defects, Atrial/Adverse effects" [Mesh] OR "Septal Occluder Device/Adverse effects" [Mesh] | 20      |
| Google   | atrial septal defect AND ASD AND Septal Occluder Device OR septal occluder OR occluder OR closure AND complications OR adverse effects OR safety AND children OR pediatric | 100     |
| ScienceDirect | atrial septal defect AND ASD AND Septal Occluder Device OR septal occluder OR occluder OR closure AND complications OR adverse effects AND pediatric | 100     |
| Total    |        | 220     |

Eligibility Criteria

The inclusion and exclusion criteria for filtering papers are listed below in Table 2.

| Inclusion Criteria | Exclusion Criteria |
|--------------------|-------------------|
| - Free full text   | - Unacceptable free full text |
| - Papers published in the last five years (2017-2022) | - Papers published before 2017 |
| - Studies done in children (birth-18 years) | - Studies with results not specific to children with ASD |
| - Articles in English language only | - Articles not in English |
| - Worldwide | - Grey literature |
| - All types of studies | - Duplicate studies |

TABLE 2: Eligibility criteria

Data Extraction

We extracted data from the included studies and recorded them under the following headings: author, year of publication, location, type of study, brand of atrial septal occluder device, sample size, age range, duration of follow-up, percentage of complete closure of the defect, sizes of ASD and occluder devices, status of septal rims, complications, intervention for complication, and associated factors in Table 3.

| Author                  | Year of publication | Location | Type of study | Device | Sample size | Age range | Follow-up | Complete Device Closure (efficacy) | ASD size | Aortic rims | Other rims | Complications |
|-------------------------|---------------------|----------|---------------|--------|-------------|-----------|-----------|-----------------------------------|----------|-------------|------------|---------------|
|                          |                     |          |               |        |             |           |           |                                   |          |             |            |               |
| (10) Mehdi Ghaderian et al | 2021               | Iran     | Cohort Study  | Biodegradable Absnow Device       | n = 35 | 6-14 months | 7.5 years | 77% (27/35) | 3.1-6.5 mm | 80% (28/35) | 80% (28/35) | 29.3% (10/35) | Right atrial or ventricular thrombosis |
| (10) Amr El-Dawalhy et al | 2021               | Egypt    | Case Report   | Amplatzer Septal Occluder         | n = 32 | 6-14 months | 7.5 years | 77% (27/35) | 3.1-6.5 mm | 80% (28/35) | 80% (28/35) | 29.3% (10/35) | Right atrial or ventricular thrombosis |
| (10) Zengying Wang et al | 2021               | China    | Case Report   | Amplatzer Septal Occluder         | n = 32 | 6-14 months | 7.5 years | 77% (27/35) | 3.1-6.5 mm | 80% (28/35) | 80% (28/35) | 29.3% (10/35) | Right atrial or ventricular thrombosis |
| (10) Zengying Wang et al | 2021               | China    | Case Report   | Amplatzers Septal Occluder        | n = 32 | 6-14 months | 7.5 years | 77% (27/35) | 3.1-6.5 mm | 80% (28/35) | 80% (28/35) | 29.3% (10/35) | Right atrial or ventricular thrombosis |
| (10) Mukiwa et al        | 2015               | India    | Subsequent Center Study | Impedent Septal Occluder | n = 12 | 6-12 months | 18 months | 77.8% (9/12) | 3 mm | 95% (11/12) | 95% (11/12) | Residual shunt (> 1.5 mm) |
| (10) Sahu Dhananjay et al| 2018               | India    | Subsequent Center Study | Impedent Septal Occluder | n = 12 | 6-12 months | 18 months | 77.8% (9/12) | 3 mm | 95% (11/12) | 95% (11/12) | Residual shunt (> 1.5 mm) |

2022 Kashyap et al. Cureus 14(5): e25402. DOI 10.7759/cureus.25402
| Author                  | Year of publication | Location | Type of study | Device | Sample size | Age range | Follow-up | Complete Device Closure (efficacy) | ASD size | Occluder size | Aortic rims | Other rims | Complications                                      |
|-------------------------|---------------------|----------|---------------|--------|-------------|-----------|-----------|-----------------------------------|----------|---------------|-------------|-----------|---------------------------------------------------|
| Yan Galatas et al      | 2019                | Greece   | Case-control  | Boston & Gore | n = 50     | 0.5 - 14 years | 10 months | Laboratory, Echocardiographic follow-up | 5.1 ± 0.4 | 7.4 ± 0.4 | -            | -            | -                                                 |
| Yilmazer et al         | 2018                | Egypt    | Cohort study  | Amplatzer   | n = 10     | 2.7 years | 10-12 months | 95%                                 | -        | Low profile ASD occluder | -           | -         | -                                                 |
| Figueira et al          | 2020                | Brazil   | Case-control  | Boston & Gore | n = 15     | 0.5 years | 10-20 months | 96% ± 3%, (280/288)                | -        | -            | -           | -         | -                                                 |
| Thanopoulos et al      | 2018                | Greece   | Prospective   | Boston & Gore | n = 25     | 2.0-14.5 years | 1-6 months | 95% ± 5%, (235/246)                  | 2± 0.5    | 3± 0.5        | Sufficient | -         | -                                                 |
| Baskar Thirumurthy et al | 2017                | Korea    | Prospective   | Boston & Gore | n = 45     | 1-16 years | 10-16 months | 95% ± 5%, (200/208)                 | -        | -            | Sufficient | -         | -                                                 |
| Zakaria et al          | 2018                | Egypt    | Case-control  | Boston & Gore | n = 7      | 0.5-14 years | 1 years | Sufficient ASD occluder | -        | -            | Sufficient | -         | -                                                 |
| Makki et al            | 2018                | Turkey   | Prospective   | Boston & Gore | n = 6      | 0.5-12 years | 1 years | Sufficient ASD occluder | -        | -            | Sufficient | -         | -                                                 |

**Note:** *ASD* = atrial septal defect, *TTE* = transthoracic echocardiography, *TTE* = transesophageal echocardiography, *AV* = aortic valve.
| Author                  | Year of publication | Location  | Type of study | Device size | Sample size | Age range | Follow-up | Closure size | Risk and Quality Assessment |
|------------------------|---------------------|-----------|--------------|-------------|-------------|-----------|-----------|--------------|-----------------------------|
| Jacinta Ng et al       | 2019                | Australia | Case Report   | n = 36       | 2.5-14y     | 3-14y     | 1 year    | 36.6%         | Risk and Quality Assessment |
| Safaa H. Ali et al      | 2017                | Egypt     | Cohort Study  | n = 135      | 0.1-14.7y   | 0.1-14.7y | 2 years   | 98.5%        | Risk and Quality Assessment |
| Mateusz T. Knop        | 2018                | Poland    | Cohort Study  | n = 132      | 20-30y      | 20-30y    | 5 years   | 98.5%        | Risk and Quality Assessment |
| Seul Gi Cha et al      | 2021                | South Korea | Cohort Study | n = 407      | 3.6-140.8m  | 3.6-140.8m| 86.7%     | 86.7%        | Risk and Quality Assessment |
| Gustaf Tanghøj et al   | 2017                | Sweden    | Retrospective | n = 252      | 0-18y       | 0-18y     | 96.5%     | 96.5%        | Risk and Quality Assessment |
| Peter J. Beck et al    | 2020                | Finland   | Retrospective | n = 135      | 2 years     | 2 years   | 94.0%     | 94.0%        | Risk and Quality Assessment |
| B. Ariendt et al 2020  | Denmark             | Denmark   | Retrospective | n = 135      | 4-21mm      | 4-21mm    | 98.5%     | 98.5%        | Risk and Quality Assessment |
| A. Debruyne et al      | 2020                | Belgium   | Retrospective | n = 135      | 5-36mm      | 5-36mm    | 95.4%     | 95.4%        | Risk and Quality Assessment |

**TABLE 3: Data extraction table**
The articles were separately screened by two reviewers (T.K. and M.S.) using various quality appraisal tools including Joanna Briggs Institute (JBI) checklist for case reports and cohort studies, Cochrane bias assessment tool for randomized control trial, and Robin’s checklist for non-randomized control trial.

Results
A total of 279,054 articles were identified after applying our search strategies: 251 from PubMed, 3,660 from Google Scholar, and 266,123 from Science Direct. A total of 220 articles remained after applying filters based on inclusion/exclusion criteria (PubMed), availability of free full text (PubMed, Science Direct), year of publication between 2017 and 2022, and including only the first 100 articles each from Google Scholar and Science Direct. Nine duplicates were found and deleted. 76 articles remained after screening based on the title and abstract, out of which 54 were excluded due to unavailability of free full text. The remaining 22 reports were assessed for quality and eligibility, leaving 21 articles total included in the review. PRISMA flow diagram is provided below in Figure 2.

Discussion
ASD closure is indicated in symptomatic children with recurrent respiratory tract diseases or failure to thrive requiring respiratory support at an earlier age, and >2 years of age in asymptomatic children weighing >15kg [18]. Transcatheter device closure of young children requires more experience and skill [18].

According to the hemodynamics, defects in patients with ratio of pulmonary blood flow to systemic blood flow (Qp/Qs) >1.5 and/or dilated right atrium and ventricle are advised to be closed [8,18,24,25,29].

According to morphological features, patients must have adequate rims on echocardiographic evaluations [18].

Safety of septal occluder devices
The criterion for safety is the absence of serious adverse effects or device embolization during the follow-up period [12]. Our study found that the complications of percutaneous transcatheter device closure of ASD in children included device embolization, cardiac erosion or perforation leading to fistulas or pericardial effusion with or without cardiac tamponade, thrombosis, bleeding, valvular damage or regurgitation, arrhythmias, conduction blocks, and migraine. In various ASD occluder devices such as the Amplatzer, Occlutech, Solyte, and Gore Cardioform Septal Occluders. The complications per study and associated factors are enumerated in Table 3. An overview of the complications and percentage of sample size with the complications is provided in Table 4.

| Author                      | Device embolization | Cardiac erosion/perforation | Pericardial effusion | Hemopericardium | Cardiac Tamponade | Fistula | Mitral valve damage/compression/contact | MR | AR | PR |
|-----------------------------|--------------------|-----------------------------|----------------------|-----------------|------------------|---------|-----------------------------------------|----|----|----|
| Yifan Li et al              | ✔️                 | -                           | -                    | -               | -                | -       | -                                       |    |    |    |
| Jun-Yi Wan et al            | -                  | ✔️                          | -                    | -               | -                | ✔️      | -                                       |    |    |    |
| Yasuko Onakatomi et al      | ✔️                 | ✔️                          | ✔️                   | -               | -                | -       | -                                       |    |    |    |
| Zai-Qiang Zhang et al       | ✔️                 | ✔️                          | ✔️                   | -               | -                | -       | -                                       |    |    |    |
| Wen-long Zhang et al        | ✔️                 | ✔️                          | ✔️                   | -               | -                | -       | -                                       |    |    |    |
| Bharti Sharma et al         | -                  | ✔️                          | -                    | -               | -                | ✔️      | -                                       |    |    |    |
| Mehdi Ghaderian et al       | -                  | -                           | -                    | -               | -                | -       | -                                       |    |    |    |

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers, and other sources

![PRISMA flow diagram](image-url)
| Author          | Device embolization | Cardiac erosion/perforation | Pericardial effusion | Hemopericardium | Cardiac Tamponade | Fistula | Mitral valve damage/compression/contact | MR | AR | PR |
|-----------------|---------------------|-----------------------------|----------------------|-----------------|-------------------|---------|----------------------------------------|----|----|----|
| Yunyong Nan et al |                     |                             |                      |                 |                   |         |                                        |    |    |    |
| Pag Peter et al  |                     |                             |                      |                 |                   |         |                                        |    |    |    |
| Knop et al.      |                     |                             |                      |                 |                   |         |                                        |    |    |    |
| Thanopoulos et al|                     |                             |                      |                 |                   |         |                                        |    |    |    |
| Mata et al.      |                     |                             |                      |                 |                   |         |                                        |    |    |    |
| Chat et al.      |                     |                             |                      |                 |                   |         |                                        |    |    |    |
| Chahat et al.    |                     |                             |                      |                 |                   |         |                                        |    |    |    |
| Hammad et al.    |                     |                             |                      |                 |                   |         |                                        |    |    |    |
| Khatib et al.    |                     |                             |                      |                 |                   |         |                                        |    |    |    |
| Khairul et al.   |                     |                             |                      |                 |                   |         |                                        |    |    |    |
| Tung et al.      |                     |                             |                      |                 |                   |         |                                        |    |    |    |
| Shakir et al.    |                     |                             |                      |                 |                   |         |                                        |    |    |    |
| Demir et al.     |                     |                             |                      |                 |                   |         |                                        |    |    |    |
| Zayed et al.     |                     |                             |                      |                 |                   |         |                                        |    |    |    |
| Zakaria et al.   |                     |                             |                      |                 |                   |         |                                        |    |    |    |

**TABLE 4: Complications of septal occluder devices**

- **MR** = mitral valve regurgitation; **AR** = aortic valve regurgitation; **PR** = pulmonic valve regurgitation; **TR** = tricuspid valve regurgitation; **AV** = atrioventricular; **AV** = atrioventricular; **AV** = atrioventricular.

[Add et al.'s study found that children <15 kg and children with large defects >30mm² were more at risk for both periprocedural and long-term complications [11].] Tanghoj et al.'s study also noted more complications in children <15 kg than those >1 kg [26]. Procedure-related challenges in young children <15 kg include smaller sized vessels and atrial septums with increased difficulty in manipulation of catheters in the heart, ASD calibration with balloon catheter, oblique position of implant in ASD after opening the left atrial disk, and lack of patient cooperation requiring longer sedation time [27]. Three of the studies included children with comorbidities such as other cardiac conditions, genetic abnormalities, and protein profiles [26,27,29]. Knop et al.'s study even included children who underwent other interventions simultaneously along with...
Atrial septal defect (ASD) closure [19]. Tanghøj et al.'s study found that 10% (n = 11) of children that weighed <15kg, 14% (n = 3) of those with other cardiac comorbidities, 16% (n = 4) that had genetic abnormalities, 15% (n = 6) that had other comorbidities, and 7% (n = 5) that were born prematurity had major complications, and none of them had minor complications except for 1% (n = 1) of 122 children [19]. The same complications were seen in both children with and without cardiac comorbidities and those without, and presence of comorbidities does not seem to be associated with greater risk of complications.

Cardiac erosion

Among the listed complications, cardiac erosion/perforation was rare, but found to be the most notable and serious, particularly seen after deployment of Amplatzer Septal Occluder. Forty percent of cases of cardiac erosion are reported in children [9]. Possible risk factors for the erosion include deficient rims, oversized device, impingement of atrial disks over aortic root, and extreme movement of device before release. Most of the cardiac erosions occur near the aortic root and the tip of the atrium [9]. After device closure of ASD, atrial erosion decreases as a result of the occluding device scraping space within it [8]. During cardiac cycle, the septal occluder device (particularly in larger size) can come in contact with and erode through the atrial roof and adjacent aorta [10]. Early erosion may only present with a small amount of periatrial effusion [14]. With growth of the child, the size of the device to the atrial septal diameter decreases, so late erosions/perforations were found to be rare [14].

Three case reports each depicted cardiac erosion in children 5-7 years of age with absent/diminished aortic rims, one month, five months, and one month respectively after transcatheter closure of ASD with Amplatzer Septal Occluder [12,14,15]. Zhang et al. also presented a case of an adolescent with cardiac erosion three months after the placement of Amplatzer Septal Occluder for closure of ASD with sufficient rims [15]. Among these four case reports of cardiac erosion, one patient subsequently developed a fistula from the aorta to the right atrium, and the other three had pericardial effusion and either hemopericardium or cardiac tamponade along with shock [12,14,15]. Al-Ali et al. and Ackermann et al. both reported cardiac erosion in some of the children who underwent transcatheter closure of ASD using various brands of occluder devices [12,16]. In Al-Ali et al.'s study, two of 151 patients developed hemopericardium and cardiac tamponade, among which only one had cardiac erosion [20]. In Ackermann et al.'s study of 370 children, two developed cardiac erosion, one of which led to the formation of a fistula (a similar finding to Al-Ali et al.'s case report), three had impairment of neighboring cardiac structures, and two presented with pericardial effusion without cardiac erosion, all within 24 hours of occluder device employment [20]. Though the remaining cohort studies included in this review did not report cardiac erosion, it cannot be ruled out as a possible future complication due to the delay in its presentation, as cardiac erosion can occur up to even nine years after device closure of ASD, and some cases of erosion may also remain undetected and spontaneously resolve [15].

Over-sized devices are sometimes chosen to close large defects with deficient aortic rims in order to cover the entire area of the defect [16]. Overstiffness of the balloon during balloon-staging of the atrial septal defect may also result in the selection of larger devices than necessary [20]. In two of the case reports of cardiac erosion, the occluder devices were used each 4mm larger than the defect, and in another case report, the device was double the size of the defect [12,15]. However, in Zhang et al.'s study, the child with deficient aortic rims was managed with a device equal in size to the defect and still developed aortic erosion, suggesting that aortic rims may be associated with higher risk of erosion than the use of an oversized device [20]. Thorpepeck et al. studied a group of 890 children with transcatheter closure of ASD in 1,371 children did not exclude children with isolated rim deficiencies, and states that risks and complications related to the procedure could be avoided if the investigator selects an appropriate implantation strategy for each individual patient [21]. Their study followed-up the children for 2-14 years and did not observe cardiac erosion in any of the other major complication [21].

Device embolization

Device embolization/occluder dislodgement is a rare but serious complication of devices closure operations [19]. A total of 37 out of 2,710 children in eight of the studies experienced device embolization after transcatheter device closure of large defects or defects with insufficient septal rim either intra or postoperatively which had to be replaced or surgically removed with or without surgical patch closure of ASD [9, 11, 19, 21, 22, 25, 27, 29, 30]. The most cases of device embolization or migration were seen in Jalal et al.'s study [22]. Out of 1,226 children, 17 experienced device embolization - seven during the procedure and 10 post-operatively [19]. Their study also had the highest frequency of rim deficiencies compared to the other studies, which could be the major contributing factor for this complication [19]. Implant embolization could also be related to the operator's learning curve [29]. Apart from device embolization, Hal et al.'s study also reported intraprocedural issues such as unstable device in three patients, requiring complex manipulation with larger devices, and oblique position of the device on a relatively large defect in one patient, requiring device removal and surgical closure of ASD one week later [21]. Intracardiac devices were also used in five more patients in Jalal et al.'s study, leading to failure of implantation [19].

Thrombosis and transient ischemic attack/stroke

In Zhang et al.'s case report, a red thrombus was incidentally found attached to the aortic wall and root of aorta during intraoperative exploration after median sternotomy to remove the occluding device due to another complication (pericardial effusion and hemopericardium) [14]. Ackermann et al. also found children with thrombus formation [20]. One of the 55 children in Gaudesius et al.'s cohort study had a central thrombosis presenting with seizure about eight hours after closure of ASD with Amplatzer Septal Occluder, followed by right-sided hemiparesis [11]. This patient had a larger defect and a longer duration of stay than the other patients [11]. Right sided hemiparesis was also observed in another patient with left hemispheric infarct following implantation of a 15mm Solysafe Septal Occluder device into an 8mm defect [20]. In Jalal et al.'s study, 5.32% children who underwent transcatheter device closure of ASD using the Amplatzer Septal Occluder, two patients presented with transient ischemic stroke on anti-platelet therapy and without thrombus three months after transcatheter device closure of ASD [20].

Valve damage/regurgitation

Among 1,607 patients aged 2-5 years in a study by Zhu et al. who underwent transcatheter device closure of ASD using various different brands of septal occluder devices, three patients had failure of closure due to compression of the mitral valve by the left atrial disk, one of which developed anterior mitral leaflet prolapse with mitral regurgitation, and the other two developed mild regurgitation [22]. In another patient, the left atrial disk of the device was touching the mitral valve [22]. Knepfl et al.'s study found mild mitral valve insufficiency in two of 157 patients under three years of age with secundum ASD who were managed with either Amplatzer Multi-FOcused Septal Occluder or Cardi-O-Fix ASD Occluder [26]. Patients in Sato et al.'s study experienced the widest variety of valvular problems compared to the rest of the studies [13-15]. Out of 1,326 children, 17 experienced device embolization - seven during the procedure and 10 post-operatively [19]. Their study also had the highest frequency of rim deficiencies compared to the other studies, which could be the major contributing factor for this complication [19]. Implant embolization could also be related to the operator's learning curve [29]. Apart from device embolization, Hal et al.'s study also reported intraprocedural issues such as unstable device in three patients, requiring complex manipulation with larger devices, and oblique position of the device on a relatively large defect in one patient, requiring device removal and surgical closure of ASD one week later [21]. Intracardiac devices were also used in five more patients in Jalal et al.'s study, leading to failure of implantation [19].

Arrhythmias and conduction abnormalities

Arrhythmias were found to be the most common minor complication among the included studies. Although ASD is known to alter atrial structure and depolarization, leading to increased risk of arrhythmias, transient arrhythmias such as supraventricular tachycardia, extras, and conduction abnormalities such as atrioventricular block have been seen after the closure of ASD [24]. Ghaderian et al. reported two cases of paroxysmal supraventricular tachycardia during placement of Amplatzer Septal Occluder device that resolved spontaneously without treatment [19]. One patient in Yilmaz et al.'s study developed junctional rhythm with pronounced after placement of Solysafe Septal Occluder which spontaneously resolved [13]. In Tanghøj et al.'s study of 252 infants undergoing transcatheter closure of ASD using various brands of occluder devices, two developed major arrhythmia requiring treatment, one developed prolonged arrhythmia during the procedure, and four developed minor arrhythmias [14]. Out of 45 children undergoing transcatheter closure of ASD with Amplatzer Septal Occluder in Qiu et al.'s study, 11 developed transient
artifact:conduction abnormalities postoperatively, including first-degree atrioventricular block (AVB I) and frequent ventricular premature beats in three patients, and atrial fibrillation in two patients. [27] 4. Jialal et al.’s study also found two cases of intra-procedural reversible atrioventricular block, and five more cases of conduction abnormality after the procedure, among which two had complete AVB block, two had AVB-II, and one had AVB-III. [19], three of them resolved either spontaneously or with symptomatic interventions, and two patients required surgical device removal [20]. They also found eight cases of arrhythmias after the procedure, three of which persisted till the last follow-up. [17] Thanopoulos et al.’s study of 1,155 children undergoing device closure with Classic Septal Occluder noted 31 patients with atrial arrhythmias during the procedure which increased to 33 cases of minor atrial arrhythmias at six months of follow-up, and one case of conduction block during the procedure, one of which was complete AVB block, while the remaining were either first or second degree AVB (AVB I or II). [22] Two more children in Cha et al.’s study developed complete AVB block, one of which was during the procedure, leading to occlusion failure [20]. Sharma et al.’s study of 45 children weighing ≤ 10 kg noted two cases of conduction abnormality after the deployment of Amplatz Septal Occluder device [11]. One child developed a transient Mobitz Type I AV block immediately after placing the occluder device, which normalized after treatment with IV isosorbide and droperidol [17]. The other child developed 2:1 AV block 24 hours after placing the occluder device, which normalized after treatment with oral isosorbide and NSAIDs [17].

**Infective endocarditis**

Ng et al. presented a case of CryoCath endocarditis in an 18-year-old patient nine years after uncomplicated implantation of a septal occluder device for ASD in Australia. [16] Echo-echocardiography confirmed the presence of a vegetation at the left atrial surface [16]. ASD-closure device-related endocarditis and CryoCath endocarditis are both rare [16]. Seven of the 21 studies included in this review report that antibiotic prophylaxis was given to the children undergoing transcatheter closure of ASD, which was likely given to the children in the other studies as well, despite them not having reported it. None of them experienced infective endocarditis. It is unknown whether the child in Ng et al.’s case received antibiotic prophylaxis prior to or during the procedure [16].

**Bleeding**

Peripheral vascular injury hematoma can be seen commonly due to the requirement of peripheral vascular (innominate vein) approach for transcatheter mode of device closure of ASD [20]. Hematoma at the access site (groin) was reported in three patients in Qas et al.’s study, two patients in Mahmoud et al.’s study, and three patients in Tham et al.’s study. [20,22]. All 11 et al.’s study had one patient with rebleeding at the access site [20]. One patient in Ackermann et al.’s study developed thrombosis of the right femoral artery. [20]. Blood also occurred in three more patients in Thanopoulos et al.’s study of which two were major and required transfusion. [20]. Another patient in Koo et al. et al.’s study required transfusion due to anemia. [20]. Abnormal was also seen in the patient with cardiac erosion and fistula in Wan et al.’s study [15].

**Hypotension and pulmonary hypertension**

In Thanopoulos et al.’s study, blood pressure drop was seen intra-procedurally in two patients, one of which required treatment, and pulmonary hypertension crisis was seen in one patient. [28] Pulmonary hypertension also was seen in two more patients in Jialal et al. et al.’s study one month after device deployment [19].

**Migraine/headache**

Migraine was reported in two of the studies. In Thanopoulos et al.’s study, 25 children developed mild to moderate migraine within 1-3 weeks of Classic Septal Occluder implantation and were managed with oral medications [16]. Fifteen children in Jialal et al.’s study had migraine as a delayed complication after Amplatz Septal Occluder implantation [19].

**Comparison of different brands of septal occluders**

As the Amplatz Septal Occluder was the most commonly employed device for the closure of ASD, it is presented with the widest range of complications overall. Complications seen with the use of Classic Septal Occluder included arrhythmias and conduction abnormalities, vascular access site problems, migration, and even device embolization in two patients [22]. Children in one study using Solysafe Septal Occluder mostly experienced valvular regurgitation [24]. Four out of 25 children in one study using Sfuello Septal Occluders experienced device embolizaton, stroke leading to hemiparesis, arrhythmias, or vascular access site problems [21]. The remaining studies used various different septal occluders, the most common being the Amplatz Septal Occluder, and displayed an array of complications.

Most of the major complications such as device embolization, or cardiac erosion/perforation and its accompanying complications are associated with larger sized septal defects with insufficient rims, particularly in those and inoperable children. These can be avoided with careful assessment of anatomical and morphological features of the defect with appropriate selection of the device as well as method of deployment preoperatively or if deemed inadequate for transcatheter device closure. Increased experience and skill of the operating surgeon in performing percutaneous transcatheter device deployment could further reduce the risk of device complications and cardiac erosion. Determination of the size of atrial septal defect can be achieved with echocardiography alone, but if surgeons choose to perform balloon-sizing as well, they must ensure caution during balloon inflation to ascertain not to overinflate and subsequently choose a larger device for the defect. Nitrate/ivabradine insufficiency was another observed complication that could be prevented with appropriate sizing of the occluder device. Arrhythmias and conduction abnormalities were the more frequently observed complications that more often than not resolved by the end of follow-up periods with or without treatment. Complications were also discovered more frequently in children <5kg due to their small size and lack of cooperation. Surgical closure of ASD should therefore be considered instead for children with larger defects with inadequate rims, as well as symptomatic children ≥15kg. Symptomatic children with ASD are subject to reconsideration and may not require closure.

**Efficacy of septal occluder devices**

**Complete Closure**

Complete closure of ASD with the septal occluder devices was ≥ 94% in nine of the 21 studies at the end of their follow-up periods [20,19,22,16,24,25,26,28]. The percentage of complete closure at last follow-up in the remaining studies is likely attributed to smaller sample size. Failure of complete closure of the septal defect was due to larger defect size. Further details are given in Table 1.

**Residual Shunts**

Residual shunts are common complications seen in device closure operations, especially in the presence of large defects. [29] Friedl or small residual shunts ≥5 mm in size usually disappear during the follow-up period as endothelialization (tissue growth over the device) occurs, as they can be ignored [25]. Residual shunts detected by TTE are graded based on their size as mild (<0.5mm), moderate (0.5-4mm), and large (>4mm), and only large residual shunts with right ventricular enlargement are considered clinically significant [23]. Most of the studies included in this review that reported residual shunts were hemodynamically insignificant.

**Device Leakage**

Cha et al. reported 44 cases of device leakage at the end of 11 years of follow-up [25]. Compared to other studies, who did not report such complications and only included children with septal defects of at least ≤ 5mm or more in size, Cha et al.’s study had a lower cutoff value for what they defined as acceptable rims [20,16,19,22,20,25,27].

**Abbreviations**

Li et al.’s study described the use of a bioabsorbable septal occluder, the Abborre device, in the closure of
Amplatzer ccribriform septal occluder for ASD with multiple fenestrations

Poulain et al.’s study in India was exclusively done in children with multiple fenestrations (more than one defect) in the interatrial septum, so they employed the use of a single Amplatzer Cribriform Septal Occluder instead of separate devices per defect. [21] Sixteen children (2.5-10.5 yrs of age with adequate size) (and documenting results specific to the brands), is still required in order to prevent the occurrence of major complications and ensure safety in every child with ASD, as well as improve efficacy in newly emerging biodegradable devices, and in the meantime, careful clinical and echocardiographic assessment of the children with ASD should be done in order to select the appropriate device and technique of implantation, and surgical repair should be considered instead for children with larger defects.

Limitations

Our study had a few limitations primarily related to brand of occluder device and sample size. Out of the 21 studies included in this review, ten were exclusively about the Amplatzor Septal Occluder (one of which was about a device modified from the Amplatzor Occluder, and another was specifically about the Cribriform Amplatzor Septal Occluder for fenestrated defects), as it is the most widely used device. Of the remaining studies included, two were exclusively about the Occluder Septal Occluder, one of which had a small sample size. There was one study each exclusive to the Occlutech Accel Flex II and Solysafe Septal Occluder, both of which had small sample sizes. The results of the other studies were not specific to the different brands of septal occluder devices. Some of the studies also had patients lost to follow-up. Therefore, our review cannot be considered a fair representation of all the available septal occluder devices. Our study also excluded papers not written in the English language, as well as articles with unavailable full text, so it is possible that many relevant articles with valuable information could have been omitted.

Conclusions

In this systematic review, we assessed the safety and efficacy of various occluder devices. The currently available transcatheter septal occluder devices have been shown to be safe and effective in the closure of the atrial septal defect in most children, but further modifications and research in the form of clinical trials with large sample sizes of children from birth to 18 years of age, using all the available septal occluder devices (and documenting results specific to the brands), is still required in order to prevent the occurrence of major complications and ensure safety in every child with ASD, as well as improve efficacy in newly emerging biodegradable devices, and in the meantime, careful clinical and echocardiographic assessment of the children with ASD should be done in order to select the appropriate device and technique of implantation, and surgical repair should be considered instead for children with larger defects.

Additional Information

Disclosures

Conflicts of interest: In compliance with the COPE uniform disclosure form, all authors declare the following: Payment//carson info: All authors declare that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that there are no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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