A comparison of the *in vivo* neoendothelialization and wound healing processes of three atrial septal defect occluders used during childhood in a nonrandomized prospective trial

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Abstract

Objective: We prospectively investigated the neoendothelialization of transcatheter secundum atrial septal defect (ASD) closure in children receiving one of three different occluders.

Methods: Transcatheter ASD closure was performed for 44 children. The patients were divided into three groups: group I: Amplatzer, group II: Lifetech CeraFlex, and group III: Occlutech Figulla Flex II septal occluder. The data were prospectively analyzed. Markers of the three phases of wound healing were studied in all patients before and on the 1st and 10th days and 1st month post intervention.

Results: The mean age of children was 7.08±3.51 years, and the mean weight was 26.07±15.07 kg. The mean ASD diameter was 12.65±3.50 mm. Groups I, II, and III comprised 34.1%, 31.8%, and 34.1% patients, respectively. No significant differences were observed between the groups regarding patient number, age, defect size, device diameter, or total septum/device ratio ($p>0.05$). Inflammatory and proliferative phase marker levels increased following the procedure ($p<0.05$). However, scar formation markers did not change after 1 month. No significant differences in neoendothelializaton were observed among the different occluders ($p>0.05$).

Conclusion: All three devices were composed of nitinol with different surface coating techniques. Although the different manufacturing features were claimed to facilitate of neoendothelialization, no differences were observed among the three devices 1 month following the procedure. *(Anatol J Cardiol 2017; 18: 229-34)*

Keywords: secundum atrial septal defect, transcatheter closure, septal occluders, neoendothelialization, children

Introduction

Various devices have been efficiently and successfully used in the transcatheter closure of secundum atrial septal defects (ASDs). The devices most commonly used are composed of an alloy comprising nickel and titanium called nitinol; of these devices, Amplatzer atrial septal occluder (Amplatzer atrial septal occluder, St. Jude Medical, Plymouth, MN, USA) is most frequently used by clinicians. Nitinol has certain features that affect thrombogenicity and neoendothelialization; additionally, excessive intracardiac release of nickel may lead to symptoms such as nickel-related allergy and cardiotoxicity (1, 2). However, there is limited information on the use of specific devices to close ASDs regarding neoendothelialization and wound healing. In interventional implemantations, neoendothelialization by the occluders is crucial and of major clinical importance because embolization as well as marked morbidity and mortality may occur if endothelialization does not occur quickly enough and if thrombus development occurs (3–6).

Although, nitinol remains the most common metal alloy used in ASD closure procedures, manufacturers are attempting to decrease the rate of nickel release and to accelerate endothelialization using different coating and heat treatment methods (1, 2, 7). Thus, we compared markers of neoendothelialization following the use of Amplatzer septal occluder, Lifetech CeraFlex septal occluder (Lifetech CeraFlex septal occluder, Lifetech Scientific Co. Ltd., Shenzhen, China), and Occlutech Figulla Flex II septal occluder (Occlutech Figulla Flex II septal occluder, Occlutech AB, Helsingborg, Sweden).

Methods

Informed consent

An informed written consent was obtained from the parents of all patients. This study was approved by the Ethics Committee of our university.

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Table 1. Secundum atrial septal occluders

Septal occluder	Used metal	Mesh structure	Surface coating	Wire thickness	Left atrial disk	Attachment mechanism
Amplatzer	Nitinol	Polyethylene terephthalate	–	100–190 micron	Standard	Screw
Lifetech CeraFlex	Nitinol	Polyethylene terephthalate	Titanium nitride	110–215 micron	Diminished material, no hub	Loop connection
Occlutech Figulla Flex II	Nitinol	Polyethylene terephthalate	Titanium oxides	40–200 micron	Diminished material, no hub	Ball

Study population

Study Design

Fifty-one pediatric patients who underwent transcatheter ASD closure between January 2014 and August 2014 were included in this study. Inclusion criteria comprised patients suitable for transcatheter ASD closure. Exclusion criteria comprised patients who had experienced recent trauma and/or recently underwent surgery, patients with infectious diseases, patients with additional heart defects, and patients who refused to participate in the study. Additional procedures were performed in patients with additional defects. Seven patients, including three who underwent pulmonary balloon valvuloplasty, one who underwent left pulmonary branch balloon angioplasty, two who underwent transcatheter patent ductus arteriosus closure, and one who underwent surgery for fibrosarcoma, were excluded from the study due to the concern that wound healing marker levels may be elevated in them. All the patients received antiplatelet therapy for 6 months after the procedure.

Amplatzer atrial septal occluder, Lifetech CeraFlex septal occluder and Occlutech Figulla Flex II septal occluder devices were used for the transcatheter closure of secundum ASDs in this study. The patients were divided into three groups based on the type of occluder used: group I, Amplatzer atrial septal occluder; group II, Lifetech CeraFlex septal occluder; and group III, Occlutech Figulla Flex II septal occluder.

Sample collection and measurement

Blood samples were collected from all the patients both before and after the procedure and at 10 days and 1 month following catheterization. The samples were centrifuged, and the serum was stored at –80°C until analysis. The samples were thawed at room temperature and were stirred and studied using an enzyme-linked immunosorbent assay. Serum levels of platelet-derived growth factor, interleukin-1α, transforming growth factor-β1, vascular endothelial growth factor, fibroblast growth factor-2, matrix metalloproteinase-9, and fibroblast growth factor-1 were assessed before angiocardiography. Platelet-derived growth factor, interleukin-1α, and transforming growth factor-β1 levels were assessed in the sample collected on the first day of angiography. Vascular endothelial growth factor and fibroblast growth factor-2 levels were assessed in the sample collected on the 10th day of angiography. Matrix metalloproteinase-9 and fibroblast growth factor-1 levels were assessed 1 month after angiography.

Technical specifications of the devices

Amplatzer atrial septal occluder is the only FDA -approved device. Lifetech and Occlutech have European Confirmity approval. Each device is composed of a self-expandable nitinol wire mesh with double discs; both discs are attached to each other with a short connecting waist of 3–4 mm. Although the left atrial disc of each device is larger than the right disc, only the Amplatzer atrial septal occluder features a left atrial metal hub. Lifetech CeraFlex and Occlutech Figulla Flex II septal occluders do not have left atrium metal hubs, and this is proposed to decrease thrombogenicity and accelerate endothelialization. The devices are composed of nitinol, an alloy comprising 45% titanium and 55% nickel. This alloy is highly resilient and is characterized by superelasticity and thermal shape memory (1, 2, 8). To increase the occlusive capacity and to ensure a rapid neoendothelial development, each disc is filled with polyethylene terephthalate (Dacron). Occlutech Figulla Flex II septal occluder device is covered with golden-yellow titanium and has a markedly decreased metal load due to altered mesh method. The company proposes that these properties decrease nickel toxicity and facilitate neoendothelialization. Additionally, all metal portions of Lifetech CeraFlex septal occluder have a ceramic coating. Occlutech Figulla Flex II septal occluder devices offer the following advantages: decreased nickel ion release into the blood and endocardium, decreased thrombus formation, and more rapid endothelialization (9, 10). The technical features of the devices are presented in Table 1 and Figure 1.

Intervention details

The defect diameter, rims, and total septal lengths were measured using transthoracic echocardiography in all patients before the study; additional defects were also evaluated. Either transesophageal- or transthoracic-guided transcatheter closure procedures were performed. The femoral vein was used as the vascular pathway in all patients. The pulmonary artery pressure, shunt ratio, and pulmonary resistance were calculated for all patients during the procedure. Regarding the transcatheter closure procedure, Amplatzer atrial, Lifetech CeraFlex, and Occlutech Figulla Flex II septal occluder devices were non-randomly se-

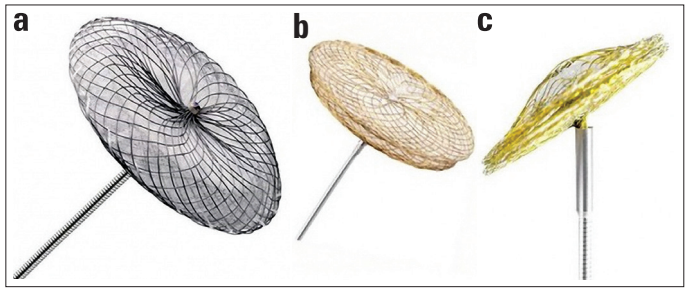

Figure 1. Images of the Amplatzer septal occluder (a), the Lifetech CeraFlex septal occluder (b), and the Occlutech Figulla Flex II septal occluder (c) devices

lected, and the numbers of patients in each group as well as the sizes of the devices were approximately equal. During the postoperative period, electrocardiography and echocardiography were performed at 1 day, 10 days, and 1 month following closure.

Mechanisms of wound healing/neoendothelialization

Wound healing is a complex process characterized by the formation of granulation tissue comprising fibroblasts embedded in a loose, collagenous extracellular matrix, newly formed blood vessels, and inflammatory cells. Neoendothelialization, angiogenesis, and exracellular matrix accumulation are the critical events that control this process (11, 12). Wound healing comprises three dynamic phases (11–13). The first phase is the inflammation/coagulation phase, which is characterized by hemostasis and inflammation; it begins immediately following the injury and ends within 24–48 h. Platelet-derived growth factor, transforming growth factors-β1 and β2, interleukin-1α, epidermal growth factor, and fibroblast growth factor levels increase during this phase. Thus, platelet-derived growth factor, interleukin-1α, and transforming growth factor-β1 serum levels were assessed on the first day of angiography. The second phase is the proliferation stage, which begins immediately following the end of the inflammatory phase and ends within 2–3 weeks. Vascular endothelial growth factor, fibroblast growth factor-2, and platelet-derived growth factor levels increase during this phase. Thus, vascular endothelial growth factor and fibroblast growth factor-2 serum levels were assessed on the tenth day of angiography. The third phase is the maturation/remodeling phase, which may occur for 2–3 weeks or up to 1–2 years. Fibroblasts proliferate at the wound site and synthesize extracellular matrix; matrix metalloproteinase-9 and fibroblast growth factor-1 and 2 levels increase during this phase (11–14). Thus, matrix metalloproteinase-9 and fibroblast growth factor-1 serum levels were assessed 1 month after angiography.

Statistical analysis

The continuous variables are expressed as the means±SDs, whereas the categorical variables are expressed as frequencies and percentages. Paired t-tests were used to compare the normally distributed parameters before and after the procedure. The characteristics of the three patient groups were compared using Kruskal–Wallis one-way analysis of variance test; $p<0.05$ was considered to be significant. All statistical analyses were performed using the Statistical Package for Social Sciences, version 22.0 (SPSS, Chicago, IL). G*power analysis program was used for the power analysis of study markers (15).

Results

Of the 44 included patients, 28 (63.6%) were girls and 16 (36.4%) were boys. The mean ages, weights, and body surface areas of the patients were 7.08±3.5 (2–17) years, 26.07±15.1 (11–78.6) kg, and 0.92±0.3 (0.5–1.9) m^2, respectively. Fifteen (34.1%) patients were assigned to group I (Amplatzer atrial septal occluder group), 14 (31.8%) patients to group II (Lifetech CeraFlex septal occluder group), and 15 (34.1%) patients to group III (Occlutech Figulla Flex II septal occluder group). No significant differences were found among the three groups regarding age, body weight, shunt ratio, pulmonary artery pressure, device diameter, device/septum ratio, fluoroscopy time, complications, success percentage, and follow-up duration ($p>0.05$). A comparison of the demographic, echocardiographic, and hemodynamic characteristics of the patients is shown in Table 2. In group I, one patient had long QT syndrome, one patient had atrial septal aneurysm, and one patient had femoral venous trace anomaly. In group II, one patient had mild mitral valve prolapse and mild-to-moderate mitral regurgitation. In group III, one patient had atrial septal aneurysm, two patients had mild mitral valve prolapse and mild-to-moderate mitral regurgitation, one patient had mild pulmonary hypertension, one patient had persistent left superior vena cava, and one patient had cerebral palsy. All the patients except the one with long QT syndrome, who was using a beta blocker, were not using any medications.

Access was obtained via the right femoral vein in all patients. Multiple defects were observed in 11 (25%) patients, and a single device was used in each case. Transesophageal echocardiography was performed in 6 (13.6%) patients. All procedures, except one, were performed under sedation. For closure of ASDs, left upper pulmonary vein technique was used in only two patients, and the standard technique, which entails opening the device in the left atrium and pulling it toward the septum, was used in the remaining patients. Sizing balloons were utilized in all patients. The diameters of the secundum ASDs were echocardiographically measured using the stop-flow technique. All procedures were successful. None of the patients developed major complications, but procedure-related transient complications were observed in two patients. One patient developed transient supraventricular tachycardia due to catheter manipulation when the defect was closed using the left upper pulmonary vein technique; this complication was corrected following manipulation of the catheter. The other patient developed transient atrioventricular dissociation when the device was withdrawn following a failed attempted closure using the standard technique. Intravenous steroids and atropine were administered, which re-

Table 2. Patients' demographic, echocardiographic and hemodynamic characteristics and comparisons

	Total (n=44)	Group I (ASO, n=15)	Group II (CSO, n=14)	Group III (OSO, n=15)	*P*
Age, years	7.08±3.5 (2–17)	7.02±3.3 (2.5–13)	8.08±4.5 (3.5–17)	6.20±2.4 (2–12)	0.365
Gender	28 girl (63.6%)	10 girl (66.7%)	6 girl (42.9%)	12 girl (80%)	0.110
Weight, kg	26.07±15.1 (11–78.6)	25.65±14.1 (11–55)	31.70±20.2 (13.7–78.6)	21.25±7.9 (11,1–41)	0.176
ASD diameter on echo, mm	12.65±3.5 (8–24)	12.86±2.9 (9–18)	13.42±3.3 (9–20)	11.73±4.1 (8–24)	0.421
Stop-flow ASD d with SB, mm	13.22±4.0 (7.8–24)	12.37±2.7 (8.2–16.3)	14.22±4.9 (9.5–24)	13.13±4.1 (7.8–23)	0.468
Multiple ASDs, %	11 (25%)	4 (26.6%)	2 (14.2%)	5 (33.3%)	0.507
Shunt ratio	1.82±0.5 (1.1–4)	1.80±0.4 (1.2–2.5)	1.95±0.8 (1.1–4)	1.70±0.3 (1.2–2.4)	0.567
PAP, mm Hg	21.73±5.3 (15–46)	22.21±3.9 (17–31)	19.66±3.1 (15–26)	22.93±7.3 (16–46)	0.269
Total septal length, mm	43.76±5.5 (32–57)	44.33±6.2 (32–57)	45.84±3.9 (40–54)	41.40±5.4 (33–49)	0.092
Device diameter, mm	15.09±4.9 (8–28)	14.06±3.1 (8–18)	16.07±6.3 (10–28)	15.20±4.9 (9–24)	0.542
Total septum/device ratio	3.16±0.9 (1.5–5.4)	3.28±0.8 (2.2–4.7)	3.22±1.0 (1.7–4.5)	2.97±1.0 (1.5–5.4)	0.254
Fluoroscopy time, min	6.58±4.1 (2.5–21.9)	6.60±3.4 (2.5–13.9)	7.71±5.9 (4–21.9)	5.50±2.4 (2.8–12.7)	0.373
Systolic pressure, mm Hg	30.21±7.7 (20–63)	31.14±5.0 (24–42)	27.00±5.7 (20–39)	31.93±10.3 (21–63)	0.121

ASD - secundum atrial septal defect; d - diameter; PAP - pulmonary artery pressure; SB - sizing balloon

stored the normal sinus rhythm after 3 min, and the defect was subsequently closed using left upper pulmonary vein technique. Before discharge, defect closure was confirmed in all patients, none of whom exhibited residual flow. No complications were observed during the follow-up period.

When the markers of neoendothelialization were compared, platelet-derived growth factor was found to be significantly increased following closure; transforming growth factor-β1 was increased during the first phase of wound healing, whereas vascular endothelial growth factor and fibroblast growth factor-2 were increased during the second phase of wound healing ($p<0.05$). No significant differences were observed in the levels of other markers with respect to the three devices ($p>0.05$). A comparison of the levels of the parameters of neoendothelialization before and after ASD closure is shown in Table 3. The power of the study was found to be between 52%–99% for wound healing markers.

No significant differences were found in the endothelialization rates among the three devices. A comparison of the neoendothelialization markers before and after ASD closure is presented in Table 4 for the three septal occluder devices.

Table 3. A comparison of the markers of neoendothelialization before and after transcatheter ASD closure

	Before	After	*P*
PDGF, pg/mL	0.091±0.09	0.150±0.05 (0–0.48)	0.003* (0.06–0.36)
TGF-β1, pg/mL	0.150±0.23	0.269±0.26 (0.02–1.13)	0.032* (0.02–1.0)
IL-1α, pg/mL	0.015±0.01	0.014±0.01 (0–0.04)	0.573 (0–0.6)
VEGF, pg/mL	0.130±0.16	0.531±0.41 (0.05–0.86)	0.001* (0.06–1.6)
FGF-2, pg/mL	0.175±0.20	0.308±0.20 (0–0.88)	0.005* (0–0.77)
MMP-9, pg/mL	0.105±0.12	0.097±0.03 (0.04–0.91)	0.671 (0.02–0.16)
FGF-1, pg/mL	0.141±0.13	0.131±0.13 (0–0.67)	0.674 (0.02–0.68)

FGF - fibroblast growth factor; MMP-9 - matrix metalloproteinase-9, PDGF - platelet-derived growth factor; TGF-β1 - transforming growth factors β1; IL-1α - interleukin-1α; VEGF - vascular endothelial growth factor; *statistically significant

Discussion

Although numerous devices may be used for percutaneous secundum ASD closure, no studies have compared the *in vivo* neoepithelialization/wound healing features of these devices.

Xu et al. (16) investigated 10 patients who underwent transcatheter closure procedures due to atrial and ventricular septal defects and patent ductus arteriosus. They analyzed endothelial progenitor cell numbers and vascular endothelial growth factor levels both before and 24 h after the above-mentioned procedures. Increased progenitor cell numbers were not observed in the majority of patients; however, increased numbers were observed among the patients who underwent transcatheter ventricular septal defect closure. Prolonged fluoroscopy time and repeated catheter manipulation may cause increased endothelial progenitor cell numbers. In the aforementioned study, the endothelial progenitor cell numbers were positively correlated with vascular endothelial growth factor levels following ventricular septal defect closure. On the premise of that study, we aimed to investigate the neoendothelialization of transcatheter secundum ASD closure in children receiving one of the three different occluders. Seven patients with additional defects who underwent additional procedures were excluded

Table 4. Comparison of the markers with respect to the Amplatzer, Lifetech CeraFlex, and Occlutech Figulla Flex II devices before and after transcatheter ASD closure

Parameters	Atrial septal occluders			*P*
	Amplatzer	Lifetech CeraFlex	Occlutech Figulla Flex II	
PDGF, pg/mL				
Before	0.079±0.11	0.076±0.04	0.117±0.11	0.469
After	0.134±0.03	0.145±0.05	0.171±0.07	0.207
TGF-β1, pg/mL				
Before	0.109±0.13	0.114±0.09	0.223±0.36	0.324
After	0.286±0.25	0.225±0.26	0.295±0.27	0.748
IL-1α, pg/mL				
Before	0.016±0.01	0.016±0.01	0.014±0.01	0.731
After	0.013±0.01	0.017±0.01	0.012±0.01	0.448
VEGF, pg/mL				
Before	0.101±0.09	0.076±0.02	0.209±0.24	0.058
After	0.444±0.43	0.591±0.43	0.563±0.38	0.601
FGF-2, pg/mL				
Before	0.165±0.19	0.124±0.12	0.232±0.27	0.378
After	0.341±0.21	0.328±0.19	0.256±0.21	0.499
MMP-9, pg/mL				
Before	0.080±0.03	0.140±0.22	0.097±0.03	0.436
After	0.097±0.02	0.094±0.03	0.099±0.03	0.908
FGF-1, pg/mL				
Before	0.144±0.14	0.129±0.09	0.148±0.15	0.926
After	0.138±0.10	0.120±0.10	0.135±0.18	0.935

FGF - fibroblast growth factor; MMP-9 - matrix metalloproteinase-9, PDGF - platelet-derived growth factor; TGF-β1 - transforming growth factor-β1; IL-1α - interleukin-1α; VEGF - vascular endothelial growth factor

from the study due to concern that levels of wound healing markers may be elevated in them.

Only limited histopathological data are available regarding the utility of different devices for ASD closure (17). Previous studies pertaining to this topic primarily comprised animal trials or evaluations of the devices in patients who underwent a procedure for other reasons. The conditions used in animal trials are generally less natural than those associated with human studies. Artificial defects are often created in experimental animals, and differences between these artificial defects and natural defects may affect both the healing process and immune response following device implantation. Sigler et al. (5) examined implants inserted into 32 animals and 12 humans with secundum ASDs. Implantation durations of the devices (14 Amplatzer, 3 Cardioseal, and 27 Starflex) ranged between 5 days and 48 months. The authors' stated the following reasons for device removal: malpositioning, valve regurgitation, repeated transient ischemic attacks, residual shunting, and device shape distortions. Fibrin, dense plasma proteins, and blood accumulated around the polyester mesh of the implants removed during the early phase of wound healing, whereas evenly distributed neoendothelial layers with shiny surfaces were observed on the implants removed between 30 days to 2 months following implantation. Additionally, no differences were observed between the animal and human trials regarding neoendothelialization, thrombus formation, and immune responses. In this study, no significant differences were found among the devices at the histological level (5). Similar to this previous study, we detected no significant differences in the endothelialization rates among the three devices in our study.

In both animal and human studies in which devices were removed, neoendothelialization began approximately 1 month after transcatheter closure. Studies have been conducted using classical staining, electron microscopy, and immunohistochemical staining (4–6). In our study, we observed increased inflammation and proliferation *in vivo* within the first weeks. Regarding matrix metalloproteinase-9 and fibroblast growth factor-1, markers of third phase of wound healing, no increase was observed from pre-procedure levels to levels after 1 month. More importantly, our study, which assessed the difference in epithelialization between the devices, indicates that heat treatment, which is conducted to accelerate endothelialization and oxidation, does not affect the stages of inflammation and proliferation. Repeating these measurements could be considered for the maturation stage. Additionally, the follow-up duration could be too short to assess the thrombus-blocking ability of Lifetech CeraFlex and Occlutech Figulla Flex II septal occluder devices due to the lack of left atrial hubs.

Study limitations

A limitation of this study was the impossibility of performing both macroscopic and microscopic examinations of neoendothelialization in our patients. The other major limitation of this study was its nonrandomized design. Also, 1 month follow-up duration could be too short to assess the neoepithelialization maturation phase markers.

Conclusion

During childhood, transcatheter septal occluder closure of secundum ASDs using an Amplatzer, Lifetech CeraFlex, or Occlutech Figulla Flex II device results in significantly increased levels of markers of both inflammation and proliferation irrespective of the device used. Neoepithelialization maturation phase markers did not differ within 1 month, possibly because the follow-up period was too short. Additionally, no significant differences were observed among the devices with respect to neoendothelialization within 1 month. This study was the first *in vivo* investigation of these processes to compare specific ASD closure devices.

Impact on daily practice

We investigated neoendothelialization *in vivo* following the placement of different occluders in children. Although these devices have different properties that are intended to promote neoendothelialization and reduce negative effects, no differences were found among them in terms of inflammatory and proliferative markers.

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References

1. Huang Y, Kong JF, Venkatraman SS. Biomaterials and design in occlusion devices for cardiac defects: a review. Acta Biomater 2014; 10: 1088-101. [CrossRef]
2. Ries MW, Kampmann C, Rupprecht HJ, Hintereder G, Hafner G, Meyer J. Nickel release after implantation of the Amplatzer occluder. Am Heart J 2003; 145: 737-41. [CrossRef]
3. Anzai H, Child J, Natterson B, Krivokapich J, Fishbein MC, Chan VK, et al. Incidence of thrombus formation on the CardioSEAL and the Amplatzer interatrial closure devices. Am J Cardiol 2004; 93: 426-31. [CrossRef]
4. Sigler M, Jux C, Ewert P. Histopathological workup of an Amplatzer atrial septal defect occluder after surgical removal. Pediatr Cardiol 2006; 27: 775-6. [CrossRef]
5. Sigler M, Jux C. Biocompatibility of septal defect closure devices. Heart 2007; 93: 444-9. [CrossRef]
6. Foth R, Quentin T, Michel-Behnke I, Vogt M, Kriebel T, Kreischer A, et al. Immunohistochemical characterization of neotissues and tissue reactions to septal defect-occlusion devices. Circ Cardiovasc Interv 2009; 2: 90-6. [CrossRef]
7. Zhang D, Zhang Z, Zi Z, Zhang Y, Zeng W, Chu PK. Fabrication of graded TiN coatings on nitinol occluders and effects on *in vivo* nickel release. Biomed Mater Eng 2008; 18: 387-93.
8. Kong H, Wilkinson JL, Coe JY, Gu X, Urness M, Kim TH, et al. Corresive behavior of Amplatzer devices in experimental and biological enviroments. Cardiol Young 2002; 12: 260-5. [CrossRef]
9. Krizanic F, Sievert H, Pfeiffer D, Konorza T, Ferrari M, Hijazi Z, et al. The Occlutech Figulla PFO and ASD occluder: a new nitinol wire mesh device for closure of atrial septal defects. J Invasive Cardiol 2010; 22: 182-7.
10. Fizser R, Szkutnik M, Chodor B, Bialkowski J. Preliminary experience in the use of CERA Occluders for closure of different intracardiac and extracardiac shunts. J Invasive Cardiol 2014; 26: 385-8.
11. Sinno H, Prakash S. Complements and the wound healing cascade: an updated review. Plast Surg Int 2013; 2013: 146764. [CrossRef]
12. Demidova-Rice TN, Hamblin MR, Herman IM. Acute and impaired wound healing: pathophysiology and current methods for drug delivery, part 1: normal and chronic wounds: biology, causes, and approaches to care. Adv Skin Wound Care 2012; 25: 304-14 [CrossRef]
13. Reinke JM, Sorg H. Wound repair and regeneration. Eur Surg Res 2012; 49: 35-43. [CrossRef]
14. Mirastschijski U, Schnabel R, Claes J, Schneider W, Agren MS, Haaksma C, et al. Matrix metalloproteinase inhibition delays wound healing and blocks latent transforming growth factor-β1 promoted myofibroblast formation and function. Wound Repair Regen 2010; 18: 223-34. [CrossRef]
15. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. Behav Res Methods 2009; 41: 1149-60. [CrossRef]
16. Xu MG, Meng XC, Li BN, Liu C. The circulating level of endothelial progenitor cells after transcatheter closure of congenital heart disease in children. Pediatr Cardiol 2013; 34: 1344-9. [CrossRef]
17. Kreutzer J, Ryan CA, Gauvreau K, Van Praagh R, Anderson JM, Jenkins KJ. Healing response to the Clamshell device for closure of intracardiac defects in humans. Catheter Cardiovasc Interv 2001; 54: 101-11. [CrossRef]