

Efficacy and safety of a parylene-coated occluder for atrial septal defect: a prospective, multi-center, randomized controlled clinical trial

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Abstract

Background: Nitinol-containing devices are widely used in clinical practice. However, there are concerns about nickel release after nitinol-containing device implantation. This study aimed to compare the efficacy and safety of a parylene-coated occluder *vs.* a traditional nitinol-containing device for atrial septal defect (ASD).

Methods: One-hundred-and-eight patients with ASD were prospectively enrolled and randomly assigned to either the trial group to receive a parylene-coated occluder ($n = 54$) or the control group to receive a traditional occluder ($n = 54$). The plugging success rate at 6 months after device implantation and the pre- and post-implantation serum nickel levels were compared between the two groups. A non-inferiority design was used to prove that the therapeutic effect of the parylene-coated device was non-inferior to that of the traditional device. The Cochran–Mantel–Haenszel chi-squared test with adjustment for central effects was used for the comparison between groups.

Results: At 6 months after implantation, successful ASD closure was achieved in 52 of 53 patients (98.11%) in both the trial and control groups (95% confidence interval (CI): [−4.90, 5.16]) based on per-protocol set analysis. The absolute value of the lower limit of the 95% CI was 4.90%, which was less than the specified non-inferiority margin of 8%. No deaths or severe complications occurred during 6 months of follow-up. The serum nickel levels were significantly increased at 2 weeks and reached the maximum value at 1 month after implantation in the control group ($P < 0.05$ *vs.* baseline). In the trial group, there was no significant difference in the serum nickel level before *vs.* after device implantation ($P > 0.05$).

Conclusions: The efficacy of a parylene-coated ASD occluder is non-inferior to that of a traditional uncoated ASD occluder. The parylene-coated occluder prevents nickel release after device implantation and may be an alternative for ASD, especially in patients with a nickel allergy.

Keywords: Congenital heart disease; Atrial septal defect; Percutaneous intervention; Parylene; Nickel

Introduction

Percutaneous atrial septal defect (ASD) closure is a well-established cardiovascular interventional therapy that has been widely used for >three decades and has become the

first-line treatment strategy for most cases of secundum ASD in both adults and children.^[1-3] Compared with surgical thoracotomy, percutaneous ASD closure has many advantages, including avoidance of cardiopulmonary bypass, avoidance of sternotomy scar, shorter

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hospitalization, and a potentially lower incidence of post-procedural complications. However, many modern cardiac devices used for percutaneous closure are made of nitinol, an alloy consisting of nickel and titanium. Many clinical applications and follow-up results have shown that nickel and its compounds have potential toxic adverse effects on the human body, which has aroused concern about the long-term safety of nickel-containing closure devices.^[4-7] Therefore, the prevention of the release of nickel contained in nitinol alloys and improvement of the metal corrosion resistance and biological safety of the closure device are very important issues. Proposed strategies included the use of platinum-coated or bio-ceramic-coated devices that prevent the release of nickel while maintaining the same elasticity.^[8,9] In recent years, a parylene-coated occluder produced in China has been used in clinical practice. Preliminary clinical results have shown that the parylene-coated occluder has good safety and efficacy and reduces the release of nickel into the blood to some extent, but there is still a lack of evidence from prospective, multicenter, and large-scale studies. Therefore, the present study aimed to evaluate the efficacy and safety of the parylene-coated occluder by performing a prospective, multicenter, and randomized controlled clinical trial.

Methods

Ethical approval

The study complied with the *Declaration of Helsinki* and was approved by the investigational review board or ethics committee at each site. All patients provided written informed consent.

Study design

The present study was a prospective, multicenter, blind evaluation, and randomized controlled clinical trial conducted in three hospitals (Beijing Fuwai Hospital, Henan Provincial People's Hospital, and West China Hospital of Sichuan University) in China. Patients in the trial group were treated with a parylene-coated ASD occluder device (Starway Medical Technology, Inc., Beijing, China), while patients in the control group were treated with a traditional ASD occluder device (Starway Medical Technology). A non-inferiority design was used to prove that the therapeutic effect of the parylene-coated device was non-inferior to that of the traditional device. The primary efficacy indicator (success rate of ASD closure) was evaluated on echocardiography by an independent third party who was blinded to the grouping of patients to ensure the objectivity and impartiality of the evaluation results.

Study population

The study subjects were patients with ASD who met the indications for interventional therapy and agreed to be enrolled in this clinical trial.

The inclusion criteria were: (1) males or non-pregnant females aged 3 to 60 years; (2) clinical diagnosis of

secundum ASD; (3) sufficient defect margins on transthoracic echocardiography or transesophageal echocardiography (the distance to the opening of the coronary sinus, superior and inferior vena cava, and a pulmonary vein was ≥ 5 mm, and the distance to the atrioventricular valve was ≥ 7 mm); (4) indications for surgical ASD repair; (5) agreement to undergo regular follow-up evaluations as required by the study protocol; (6) provision of written informed consent.

The exclusion criteria were: (1) secundum ASD with other intracardiac malformations requiring surgical correction; (2) ASD with severe pulmonary hypertension with a bidirectional shunt; (3) active endocarditis, intracardiac vegetations, sepsis, bacteremia, and other systematic infectious diseases within 1 month before ASD treatment; (4) intolerance to oral aspirin.

Sample size and randomization

In clinical application, traditional ASD occluders achieve a satisfactory plugging effect. According to previous studies^[10,11] and the experience of the clinicians, the plugging success rate of the control group was estimated to be 98% at 6 months after occluder implantation, and the clinically acceptable non-inferiority margin was 8%; thus, with a two-sided α level of 0.05 and a power of the test ($1-\beta$) of 80%, a minimum of 50 patients were needed in each group. Considering the possibility of a 5% dropout rate and the length of the randomized block, the aim was to enroll at least 54 patients in each group. A total of 108 patients were randomly assigned to the trial group or the control group in a 1:1 ratio using a web-based allocation system [Figure 1].

Parylene-coated ASD occluder device

The device is braided from parylene-coated nitinol wires into two round discs with a 3 to 4-mm connection waist. The left atrial disc is 12 to 16 mm and the right atrial disc is 8 to 10 mm larger than the waist. The device is filled with three layers of polyester alone or polyester and expanded polytetrafluoroethylene to facilitate complete occlusion. In accordance with the different waist diameters, the device can be divided into different models with diameters of 4 to 44 mm, all of which can be delivered, positioned, and released through the same delivery system (6–14F delivery sheath) as for the traditional uncoated ASD occluder device [Supplementary Figure S1, <http://links.lww.com/CM9/A833>].

Procedure

The right femoral vein was punctured under local anesthesia (general anesthesia for children <10 years), and routine right cardiac catheterization was performed. Transthoracic echocardiography or transesophageal echocardiography was performed to assess the size, location, and relationship of the ASD to the surrounding tissues. An appropriate occluder was selected and delivered to the left atrium via a delivery sheath. Under fluoroscopic guidance, the left atrial disc was extruded. The sheath and the delivery wire were withdrawn in unison until resistance

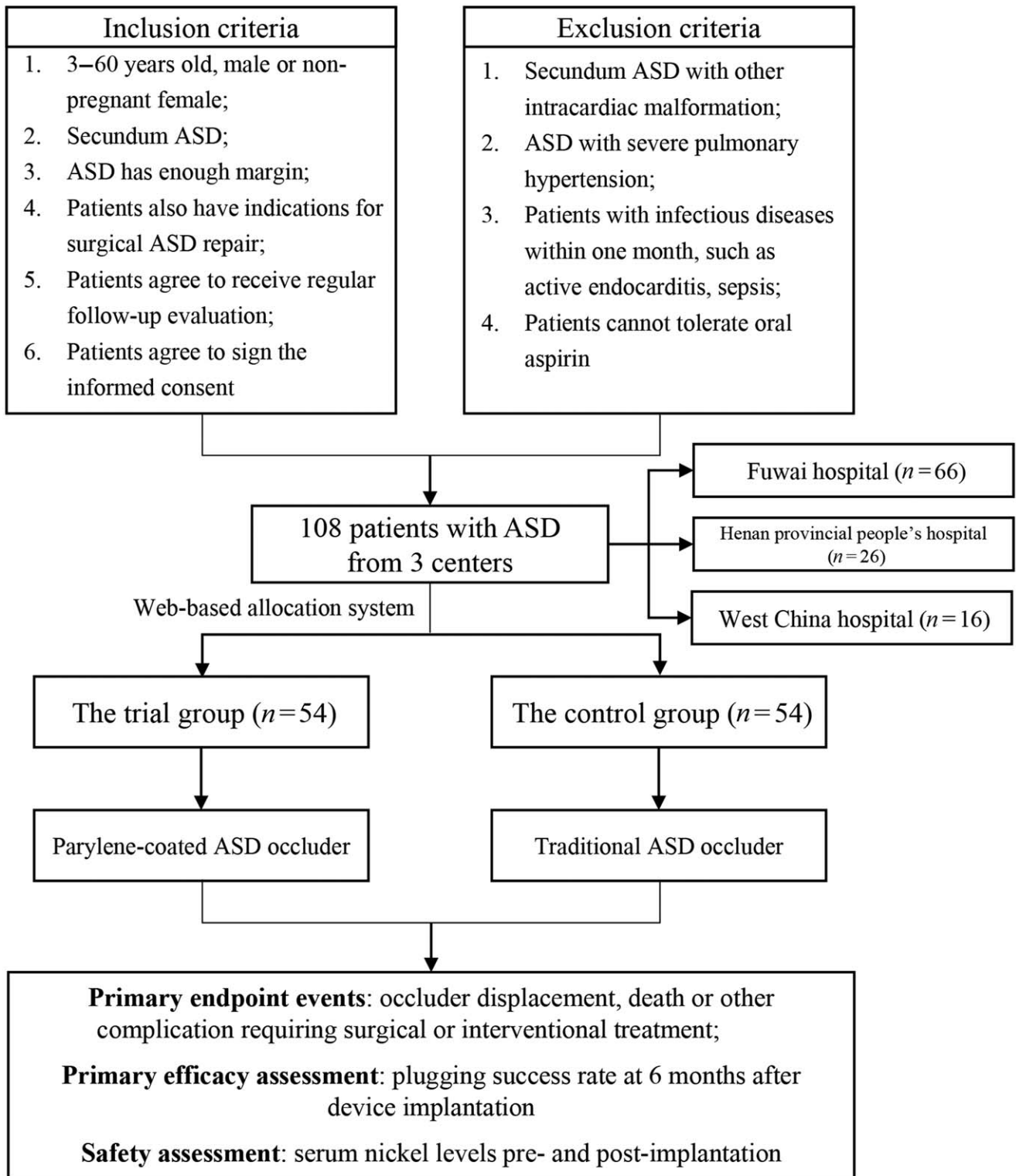


Figure 1: The study flow chart on evaluation of a parylene-coated occluder for ASD. ASD: Atrial septal defect.

was met when the extruded left atrial disc was apposed to the atrial septum. The occluder was then fully deployed by withdrawing the sheath over the delivery wire to extrude the right atrial disc. Once satisfactory occluder position and stability were achieved, the occluder was released by counterclockwise rotation of the delivery wire.

Follow-up and primary endpoint

The patients received echocardiography, chest radiography, electrocardiography, routine blood testing of liver and kidney function, and serum nickel concentration tests pre-operatively, and at 24 h, 2 weeks, 1, 2, 3, and 6 months post-operatively. The endpoint events assessed at 6 months

post-operatively included occluder displacement, death, and other complications requiring surgical or interventional treatment.

Primary efficacy and safety assessment

The primary efficacy indicator was the plugging success rate at 6 months after the ASD occluder device implantation. Successful closure was defined as no residual shunt or only a small amount of residual shunt at the plugging site (shunt beam diameter ≤2 mm on echocardiography). Safety assessment included measurements of serum nickel levels and routine blood testing of liver and kidney function at the stated time points after ASD occluder device implantation.

Statistical analysis

The full analysis set (FAS) comprised a set of subjects determined by the intention-to-treat principle and included all patients who were randomly assigned to receive treatment with the study product and underwent baseline evaluations. The per-protocol set (PPS) comprised a subset of subjects whose compliance with the protocol was sufficient to ensure that their data would likely exhibit the effects of treatment according to the underlying scientific model. The safety set (SS) comprised a set of subjects who were randomized to receive treatment with the study product and underwent at least one safety evaluation. The primary efficacy analysis was conducted using the FAS and PPS, baseline demographic data were analyzed using the FAS, and safety assessment was performed using the SS. Continuous variables were presented as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Intergroup differences were analyzed using the paired-samples *t* test for normally distributed continuous variables, and the Chi-squared or Fisher exact test for categorical variables. For primary efficacy analyses, the 95% confidence intervals (CIs) of the differences between the two groups were calculated using

the Cochran–Mantel–Haenszel Chi-squared test with adjustment for central effects. Sensitivity analysis based on different statistical analysis methods and missing value imputation methods was also performed to determine whether the results were robust. The selected non-inferiority margin was the same for both the FAS and PPS. If the absolute value of the lower limit of the 95% CI was less than the specified non-inferiority margin of 8%, then the non-inferiority conclusion was valid. All statistical analyses were performed with SAS® 9.1.3 software (SAS Institute, Cary, NC). A two-tailed *P* value < 0.05 was considered to indicate statistical significance.

Results

Study population

A total of 108 patients from three centers (Beijing Fuwai Hospital (*n* = 66), Henan Provincial People’s Hospital (*n* = 26), and West China Hospital of Sichuan University (*n* = 16)) were recruited, including 54 in the trial group and 54 in the control group [Figure 1]. During the trial, one patient (1.85%) in the trial group and one (1.85%) in the control group were lost to follow-up, and no patients seriously violated the study protocol. The FAS included 54 patients in the trial group and 54 in the control group, the PPS included 53 patients in the trial group and 53 in the control group, and the SS included 54 patients in the trial group and 54 in the control group.

Baseline characteristics

The baseline characteristics of the trial and control groups were basically balanced. There were no significant differences between the two groups in demographic data, family history, previous medical history, and history of metal allergy. Among the pre-operative clinical diagnostic indicators, there were no significant intergroup differences in other indicators except for the diameter of the ASD (*P* = 0.02). The detailed information is shown in [Table 1].

Table 1: Baseline characteristics of the trial and control groups of ASD patients.

Characteristics	Trial group (<i>n</i> = 54)	Control group (<i>n</i> = 54)	Statistical value	<i>P</i> value
Male, <i>n</i> (%)	14 (25.93)	19 (35.19)	1.09*	0.30
Age (years)	33.18 ± 16.46	27.14 ± 17.92	2.07†	0.07
BMI (kg/m ²)	21.17 ± 4.94	19.54 ± 4.09	1.73‡	0.07
Family history of CHD, <i>n</i> (%)	0	2 (3.70)	NA‡	0.50
Metal allergy history, <i>n</i> (%)	0	0	NA‡	NA
Previous medical history, <i>n</i> (%)	1 (1.85)	3 (5.56)	NA‡	0.62
Defect diameter of ASD (mm)	17.07 ± 7.23	13.92 ± 7.10	2.28‡	0.02
Distance between ASD and orifice of IVC (mm)	14.46 ± 6.76	13.39 ± 6.10	0.86‡	0.60
Distance between ASD and root of MV (mm)	12.18 ± 4.05	12.86 ± 4.57	0.82‡	0.62
RVAPD (mm)	28.21 ± 7.37	26.06 ± 9.07	1.35†	0.19
Estimated PASP (mmHg)	44.59 ± 10.51	42.38 ± 9.65	1.14†	0.44
CTR	0.51 ± 0.07	0.48 ± 0.06	2.39†	0.07

*χ² value for the chi-squared test. † *t* value for the *t* test. ‡ No statistical value for the Fisher exact test. Data was presented by mean ± SD or *n* (%). ASD: Atrial septal defect; BMI: Body mass index; CTR: Cardiothoracic ratio; CHD: Congenital heart disease; IVC: Inferior vena cava; MV: Mitral valve; NA: Not available; PASP: Pulmonary arterial systolic pressure; RVAPD: Right ventricular anteroposterior diameter.

Table 2: Comparison of the plugging success rate in the two groups at 6 months after ASD occluder device implantation.*

Parameters	Trial group	Control group
Overall population, <i>n</i>	54	54
Successful closure, <i>n</i> (%)	52 (96.30)	52 (96.30)
Unsuccessful closure, <i>n</i> (%)	2 (3.70)	2 (3.70)
CMH Chi-squared test	Difference	0 (−6.81; 7.33)
	(95% CI) [†]	

The CMH Chi-squared test with adjustment for central effects was used for the comparison between groups. *Difference in the success rate between the trial and control groups. †Based on the FAS with the missing values considered as unsuccessful closures. ASD: Atrial septal defect; CMH: Cochran–Mantel–Haenszel; CI: Confidence interval; FAS: Full analysis set.

Primary endpoint event

One patient (1.85%, 1/54) in the trial group and one patient (1.85%, 1/54) in the control group had occluder displacement 1 day after device implantation. The reasons for these two failures were errors in the measurements of the size and margin of the defect on pre-operative ultrasonography. During 6 months of follow-up, there were no deaths or severe complications requiring surgical or interventional treatments, except for incomplete right bundle branch block in two patients (3.70%, 2/54) in the trial group.

Primary efficacy

The FAS analysis (with the missing values considered as unsuccessful plugging cases) showed that 52 patients (96.30%, 52/54) had successful ASD closure and two patients (3.70%, 2/54) had a failure at 6 months post-operatively in the trial group. In the control group, the closure was successful in 52 patients (96.30%, 52/54) but unsuccessful in two patients (3.70%, 2/54) at 6 months post-operatively. The difference in the success rate between the trial and control groups was 0 (95% CI: [−6.81; 7.33]). The absolute value of the lower limit of the 95% CI was 6.81%, which was less than the non-inferiority margin of 8% specified in the trial design; thus, the non-inferiority conclusion was valid [Table 2].

The PPS analysis showed that at 6 months post-operatively, successful closure was achieved in 52 patients (98.11%, 52/53) in the trial group and 52 patients (98.11%, 52/53) in the control group, while the closure was unsuccessful in one patient (1.89%, 1/53) in the trial group and one patient (1.89%, 1/53) in the control group. The difference in the success rate between these two groups was 0 (95% CI: [−4.90; 5.16]). The absolute value of the lower limit of the 95% CI was 4.90%, which was less than the specified non-inferiority margin of 8%; therefore, the non-inferiority conclusion was valid [Table 3].

Sensitivity analysis based on different statistical analysis methods and missing value imputation methods showed that the absolute values of the lower limits of the 95% CIs were all less than the specified non-inferiority margin of 8%; therefore, the non-inferiority conclusion was valid

Table 3: Comparison of the plugging success rate between the two groups at 6 months after ASD occluder device implantation.*

Parameters	Trial group	Control group
Overall population, <i>n</i>	53	53
Successful closure, <i>n</i> (%)	52 (98.11)	52 (98.11)
Unsuccessful closure, <i>n</i> (%)	1 (1.89)	1 (1.89)
CMH Chi-squared test	Difference	0 (−4.90; 5.16)
	(95% CI) [†]	

The CMH Chi-squared test with adjustment for central effects was used for the comparison between groups. *Difference in the success rate between the trial and control groups. †Based on the PPS. ASD: Atrial septal defect; CMH: Cochran–Mantel–Haenszel; CI: Confidence interval; PPS: Per-protocol set.

[Supplementary Table S1, <http://links.lww.com/CM9/A833>]

The right ventricular anteroposterior diameter gradually decreased during follow-up after ASD occluder device implantation, indicating restored right ventricular function [Figure 2].

Safety assessment

In the trial group, the serum nickel levels were not significantly different before and after device implantation (all *P* > 0.05). In contrast, the serum levels of nickel in the control group were significantly increased at 2 weeks and reached the maximum value at 1 month after device implantation (both *P* < 0.05 vs. baseline), then gradually decreased to baseline levels during follow-up [Figure 3 and Supplementary Table S2, <http://links.lww.com/CM9/A833>].

There were no significant differences in liver and kidney function between the two groups before and after implantation of the ASD occluder device [Supplementary Table S3, <http://links.lww.com/CM9/A833>].

Discussion

Nitinol-containing devices for percutaneous transcatheter closure of ASD have been widely used for over three decades, with satisfactory and excellent results in clinical application.^[1,2] However, there are concerns about the release of nickel after nitinol device implantation. Therefore, it is very important to determine how to prevent nickel release while preserving the super-elastic and shape-memory properties of nitinol. In the present study, we used a parylene-coated nitinol device braided from nanoparylene-coated nitinol wires to prevent nickel release. The results showed that transcatheter closure of ASD using a parylene-coated occluder device can be performed safely and successfully with good results that are non-inferior to the results obtained using the traditional ASD occluder device. More importantly, the parylene-coated occluder device potentially prevents nickel release after nitinol device implantation and may be an alternative for ASD closure, especially in patients with potential nickel allergy.

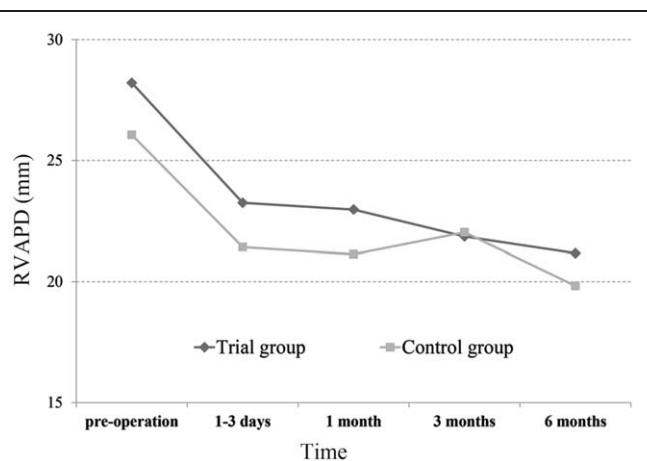


Figure 2: Change in the RVAPD during 6 months of follow-up in the trial group ($n = 52$ at 6 months) and control group ($n = 52$ at 6 months). The RVAPD gradually decreased after ASD occluder device implantation, indicating restored right ventricular function. ASD: Atrial septal defect; RVAPD: Right ventricular anteroposterior diameter.

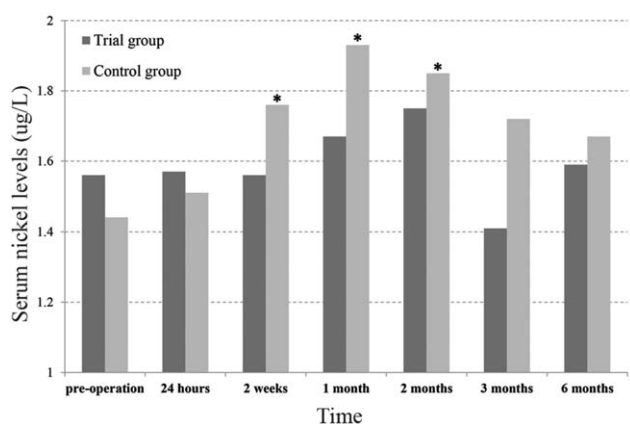


Figure 3: Serum nickel levels before and after ASD occluder device implantation in the trial group ($n = 47$ at 6 months) and control group ($n = 51$ at 6 months). * $P < 0.05$ vs. baseline levels of serum nickel in the control group. ASD: Atrial septal defect.

An ASD occluder device is one of the main implanted instruments in interventional therapy for congenital heart disease; its mechanism is to place the nitinol mesh structure containing polyester fabric in the lesion area and close the congenital defect by mechanically blocking the blood flow across the septum. The parylene-coated occluder device tested in this clinical trial is an innovation based on the traditional uncoated ASD occluder device that has been widely used in clinical practice. The structural features, production process, executive standards, specifications and models, sterilization methods, clinical indications, and operation methods of the parylene-coated occluder device are the same as for the traditional uncoated ASD occluder device except that the nitinol wire is coated with parylene. Therefore, doctors are familiar with the procedure and do not need additional skills to implant this new device. In the present study, both the trial and control groups had high successful closure rates (96.30%–98.11%), and the therapeutic effect of the parylene-coated device was non-inferior to that of the traditional device.

Previous studies have demonstrated evidence of nickel release after nitinol-containing occluder implantation.^[12-14] Ries *et al*^[12] reported a significant rise in serum nickel levels after the Amplatzer device implantation; the mean serum levels of nickel were significantly increased at 24 h and reached the peak value at 1 month after implantation, before gradually decreasing to the baseline level. Burian *et al*^[13] also reported a significant rise in both serum and urine nickel levels after implantation of a nickel device in patients with ASD; the serum nickel levels significantly increased by up to five-fold ($P < 0.01$ vs. baseline) during the 6-week post-closure period, and the mean nickel concentrations in serum and urine returned to baseline levels within 4 to 6 months post-implantation. A recent study also demonstrated a significant rise in serum nickel levels after implantation of the Amplatzer occluder; the maximum serum level of nickel was detected at 3 months after implantation and gradually returned to the baseline level during follow-up.^[14] The nickel release after implantation of nitinol-containing devices may trigger allergic reactions. Systemic adverse effects associated with nickel allergy, such as pericarditis and increased frequency of migraine headaches, have been reported in patients with transcatheter closure of interatrial shunts.^[4-7,15] In most reported cases, the symptoms resolved spontaneously or with non-steroidal anti-inflammatory therapy. However, a small number of patients with nickel allergy and severe refractory symptoms may require surgical explantation of the device.^[16-18] Moreover, research has demonstrated that nickel is cytotoxic and carcinogenic to humans.^[19,20] Proposed strategies to prevent nickel release while maintaining the same elasticity include the use of a platinum-coated device. Previous results have shown no significant difference in serum nickel levels before and after implantation, indicating that nano-coating of platinum on nitinol wires prevents nickel release following device implantation.^[8,9] Furthermore, a previous study of a ceramic-coated ASD occluder reported that the serum nickel level was significantly lower in the ceramic-coated group than the control group.^[21] However, all these previous findings were based on single-center small-sample studies.

In the present multicenter study, the ASD occluder device in the trial group was braided from parylene-coated nitinol wires. Parylene is a thermoplastic polymer material with good chemical inertness and biocompatibility that have been certified by the Food and Drug Administration and has the potential to prevent nickel release.^[22] The present results showed no increased serum levels of nickel after parylene-coated device implantation in the trial group, while implantation of the traditional device in the control group resulted in significantly increased serum levels of nickel at 2 weeks and a peak value at 1 month after implantation before gradually decreasing to baseline levels during follow-up, which was consistent with previous studies.^[12-14] These results suggest that the parylene-coated ASD occluder has the potential to prevent nickel release after device implantation, and may be a viable alternative for patients with ASD, especially those with nickel allergy.

Study limitations

This study demonstrated that the efficacy of parylene-coated occluder was non-inferior to that of the traditional occluder, and that the parylene-coated occluder device potentially prevents nickel release; however, this study also has some limitations. First, as the follow-up was relatively short, the long-term efficacy and safety of the parylene-coated ASD occluder remain unclear. Second, the mean serum nickel levels of the normal population were not assessed. Third, although this was a multicenter study, about 60% of patients were recruited in one center, decreasing the strength of the multicenter study.

Conclusions

The therapeutic effect of the parylene-coated ASD occluder is non-inferior to that of the traditional uncoated ASD occluder. In addition, the parylene-coated ASD occluder potentially prevents nickel release after device implantation and may be an alternative for patients with ASD, especially in those with nickel allergy.

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Conflicts of interest

None.

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