

VALVULAR AND STRUCTURAL HEART DISEASES

Original Studies

Interatrial Shunt Closure Devices in Patients with Nickel Allergy

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We assessed outcomes in nickel allergic patients treated with percutaneous interatrial shunt device closure with the Helex device. Nickel toxicity has been well described in patients undergoing interatrial shunt closure with the Amplatzer device, which has a nitinol design. There have been no reports using Helex in nickel allergic patients. Ninety-five consecutive patients underwent percutaneous interatrial shunt closure at a single US center by one operator. In those with possible nickel allergy, patch testing with the North American Contact Dermatitis Group standard series and a metal series was performed. The mean age was 48 ± 16 years (range 18–81), 48% were male, 21 (22%) had atrial septal defect, and 74 (78%) had patent foramen ovale. Six patients had a positive skin test to nickel and underwent successful closure with Helex. Of the remaining 89 patients, 88 were closed with Amplatzer and one with Helex. All procedures were successful with no deaths, myocardial infarctions, strokes, or systemic emboli at six-month followup. None of the Helex patients developed an allergic reaction, significant chest pain, or arrhythmia. Of those without pre-procedural known nickel allergy, 12% had palpitations, 5% had atrial fibrillation, and 13% had chest pain. When compared with a published report that 89% of nickel-allergic patients developing an allergic reaction to the Amplatzer or Premere device, Helex appeared far safer in nickel allergic patients ($P < 0.001$). In patients with nickel allergy, percutaneous interatrial shunt device closure with Helex device is safe, and is not associated with allergy to nickel. © 2009 Wiley-Liss, Inc.

Key words: nickel; allergy; device; nitinol; patent foramen ovale; atrial septal defect

INTRODUCTION

Hypersensitivity to nickel is a known entity and it may occur in up to 15% of the general population [1]. Percutaneous closure of atrial septal defect (ASD) and patent foramen ovale (PFO) patients has become a common procedure for patients with heart failure, cryptogenic stroke, and systemic emboli. Many of the interatrial shunt closure devices contain “nitinol,” which is an alloy composed of 45% titanium and 55% nickel. This alloy is widely used in medical products [2–7] because of its radiopacity, elasticity, resistance to fatigue and corrosion, and memory shape properties.

Nickel toxicity has been reported in patients undergoing interatrial shunt closure with devices constructed of nitinol. Nickel allergy has been associated with systemic adverse side effects [8], pericarditis [9,10], and increasing migraine headache in patients undergoing percutaneous closure of interatrial shunts [11]. Nickel

hypersensitivity has been shown to cause “device syndrome,” noted in eight of nine patients with known allergy to nickel, who underwent percutaneous

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TABLE I. Demographic and Clinical Data (n = 95)

Characteristic	Value
Age, years	48.2 ± 16.1 (range 18–81)
Male	46 (48%)
Atrial septal defect	21 (22%)
Qp/Qs shunt fraction	1.52 ± 0.48
Patent foramen ovale	74 (78%)
Prior stroke	51 (69%)
Prior transient ischemic attack	19 (26%)
Prior systemic embolus	2 (3%)
<i>Platypnea orthodeoxia</i>	2 (3%)

Data are presented as mean ± standard deviation for continuous variables or number (percentage) for dichotomous variables

interatrial shunt closure using either the Amplatzer (AGA Medical, Plymouth, MN) or Premere (St. Jude Medical, Inc., St. Paul, MN) devices [12].

Unlike these devices, the Helex device (W.L. Gore & Associates, Inc., Flagstaff, AZ) has a minimal amount of exposed nitinol, with the majority of the circumferential nitinol support frame enclosed in an ePTFE occlusion membrane. Given the reported high-risk of adverse outcomes in nickel allergic patients receiving the Amplatzer or Premere devices, we sought to assess the outcomes in nickel allergic patients treated with the Helex device for inter-atrial shunt closure. We compared the results from three types of patients: (1) our single-center experience of the Helex device in nickel allergic patients, (2) our experience with the Amplatzer device in those with no preprocedure known nickel allergy, and (3) the reported experience of the Amplatzer and Premere devices in nickel allergic patients [11].

MATERIALS AND METHODS

This is a retrospective, single-center cohort study, performed at the University of Utah in Salt Lake City, Utah by one experienced operator (ADM). The institutional review board approved this study's design and analysis plan. We included consecutive patients who underwent percutaneous secundum ASD or PFO closure from June 2006 through September 2008.

All patients were assessed preprocedurally with both transthoracic echocardiography and transesophageal echocardiography, including bubble study. All patients were questioned regarding a history of possible nickel allergy. Those patients who had a possible nickel allergy underwent formal cutaneous patch testing with the North American Contact Dermatitis Group standard series, as well as a metal series which included at least two different concentrations of nickel sulphate (2.5% and 5.0% in petrolatum) and three different salts of titanium (titanium nitride 5%, titanium oxalate 5%, and calcium titanate 10% in petrolatum). Readings were

performed at 48 and 72 hr. Patch testing was performed under the supervision of a dermatologist (DLP). A device allergic syndrome was defined as a postprocedure occurrence of chest pain, exertional dyspnea, and asthenia [12].

RESULTS

Of the 95 study patients, 87 had no known allergy for nickel prior to device closure, and eight underwent formal skin testing for nickel. Of these eight patients with skin testing, six patients were allergic to nickel. Each of these patients were offered surgical closure of their interatrial shunt and elected to undergo percutaneous defect closure using the Helex device. The 89 patients who either had no known nickel allergy or were negative on skin testing had defect closure using either an Amplatzer ($n = 88$) or Helex ($n = 1$) device. Demographic and clinical characteristics are described in Table I. All patients were treated with either warfarin ($n = 4$) or dual antiplatelet therapy ($n = 91$) with aspirin 81mg daily for 6 months and clopidogrel 75 mg daily for 2–6 months. Clinical and transthoracic echocardiographic follow-up was available in 100% of patients at both 1- and 6-months. At 6-month follow-up for the total cohort of 95 patients, none had death, myocardial infarction, stroke, transient ischemic attack, systemic embolus, or endocarditis.

In the group without known nickel allergy ($n = 89$), there were 2 (2%) procedural complications (Table II). One patient with a large secundum ASD had a 36 mm Amplatzer atrial septal occluder device embolization within 12 hr of device implantation, requiring percutaneous retrieval. This patient underwent successful ASD closure using a 38 mm atrial septal occluder device. A second patient with PFO and associated atrial septal aneurysm had immediate embolization of a 25 mm Amplatzer Cribriform occluder. This patient underwent successful percutaneous retrieval and subsequent successful closure using a 35 mm Cribriform occluder.

In this group without known nickel allergy, the most common symptom after the device placement was palpitations in 11 (12%). Other symptoms included atrial fibrillation in 4 (5%), minor chest pain in 7 (8%), moderate-to-severe chest pain in 4 (5%), late pericardial effusion in 2 (2%), and allergic device syndrome in one.

One of the patient who developed “allergic device syndrome” is a 51-year-old male with a cryptogenic stroke. He had no known prior allergy to nickel or other metals. He underwent successful PFO closure using a 25 mm Amplatzer Cribriform occluder. One week after device placement, he noticed new severe palpitations with associated chest discomfort. Transthoracic echocardiography showed a properly positioned

TABLE II. Comparison Based on Preprocedure Known Nickel Allergy

Group	I	II (Ref 12)	III		
Characteristic	Nickel allergy treated with Helex (<i>n</i> = 6)	Nickel allergy treated with Amplatzer/Premere (<i>n</i> = 9)	No Prior Known nickel allergy (<i>n</i> = 89)	<i>P</i> -value (I vs II)	<i>P</i> -value (I vs III)
Age, years	34.7 ± 19.3	31.3 ± 13.2	49.1 ± 15.6	0.69	0.034
Male	0 (0%)	1 (11%)	46 (52%)	0.40	0.014
Atrial septal defect	1 (17%)	5 (56%)	20 (22%)	0.13	0.83
Patent foramen ovale	5 (83%)	4 (44%)	69 (78%)	0.13	0.74
Device					<0.0001
Amplatzer Septal Occluder	0 (0%)	4 (44%)	20 (22%)		
Amplatzer Cribriform	0 (0%)	3 (33%)	68 (76%)		
Helex	6 (100%)	0 (0%)	1 (1%)		
Premere	0 (0%)	2 (22%)	0 (0%)		
Positive nickel skin test	6 (100%)	9 (100%)	1 (1%)	1.0	<0.0001
Complete closure, 6 months	6 (100%)	9 (100%)	86 (97%)	1.0	0.65
Procedural complications	0 (0%)	0 (0%)	2 (2%)	1.0	0.71
Atrial fibrillation	0 (0%)	0 (0%)	4 (5%)	1.0	0.60
Palpitations	0 (0%)	1 (11%)	11 (12%)	0.40	0.36
Chest pain, any	1 (17%)	8 (89%)	11 (12%)	0.005	0.76
Minor	1 (17%)	NA	7 (8%)	—	0.45
Moderate-to-severe	0 (0%)	NA	4 (5%)	—	0.60
Pericardial effusion	0 (0%)	0 (0%)	2 (2%)	1.0	0.71
Allergic device syndrome	0 (0%)	8 (89%)	1 (1%)	0.001	0.79

device without ventricular or valvular dysfunction, and no pericardial effusion. Holter monitoring revealed a rare atrial fibrillation (less than 1% of the recording), and frequent premature atrial complexes with aberrant conduction (8000 premature atrial beats in the 24 hr recording). He had some symptomatic improvement with beta-blocker therapy. He underwent cutaneous patch testing that showed he was allergic to nickel, gold, copper, palladium, cobalt, and manganese. The patient started prednisone to suppress the inflammatory process, with significant improvement in both his palpitations and chest pain. Over the next 6 months, several attempts to wean off the prednisone were unsuccessful, with recurrence of palpitations, chest pain, and re-flaring of the skin irritation at the nickel test site. Six months after closure, he remains on prednisone 5 mg daily without allergic symptoms.

The preprocedure nickel allergic group (*n* = 6) tended to be younger compared with the non-allergic group, and all were female (Table II). In this nickel allergic group, the indication for device placement was PFO in five and ASD in one. There were no procedural complications, and immediate, complete closure was achieved in all patients by bubble study. One patient developed minor transient chest pain, and none experienced symptoms of palpitations, moderate-to-severe chest pain, atrial fibrillation, or pericardial effusion. In comparing our nickel-allergic patients treated with Helex, to the nickel-allergic patients treated with Amplatzer or Premere reported by Rigatelli et al [12] those treated with Helex had a significantly lower prevalence of chest pain (*P* = 0.005) and device allergic

syndrome (*P* = 0.001; Table II). There were no other significant differences between the nickel allergic patients in our series compared with those from Rigatelli's report.

DISCUSSION

There are several percutaneous devices used in the United States for closure of secundum ASD and PFO. Many of these interatrial shunt closure devices contain "nitinol," which releases detectable levels of nickel into the bloodstream. Unlike the Amplatzer and Premere devices which have extensive nitinol exposed to the bloodstream, the Helex device has a minimal amount of exposed nitinol, with the majority of the circumferential nitinol support frame enclosed in the ePTFE occlusion membrane. In this article, we describe the absence of allergic symptoms in six patients with a documented nickel allergy who did not develop an allergic response to the Helex device.

Though some investigators reported no increase in the concentrations of nickel in the blood after deployment of the Amplatzer nitinol devices [13], other studies have reported that nickel is released into the blood [14,15], typically peaking 1–3 months after device implantation. Nickel is released until a calcium-phosphate layer has formed on the passive oxide film of the device or until endothelialization is completed [14]. Ries et al, in their study of 67 patients with transcatheter closure of atrial septal defects with Amplatzer device, has shown that serum nickel level increases from 0.47 ng/ml before the implantation to 1.27 ng/dl at 24 h,

and to a maximum of 1.5 ng/dl at one month after implantation. Serum nickel level continued to be elevated at 3 months, and then eventually dropped to baseline at 12 months. Burian et al [15] followed serum and urine nickel levels for 12 months in 24 patients who underwent transcatheter ASD closure with the Amplatzer device. During the 6-week postclosure period, serum nickel level increased up to 5-fold compared with the baseline. Mean concentrations of nickel in serum and urine returned to baseline levels within 4-6 months post implantation.

It should be acknowledged that the issue of nickel allergy due to transcatheter device implantation remains controversial. Although several studies have monitored urine and/or blood nickel levels following Amplatzer device insertion [13-15], there is no such data available with other devices. Although there are several case reports [8-11] of adverse patient outcomes in those with nickel allergy, the diagnostic criteria, prevalence, and correlation with skin testing for nickel allergy remains obscure. There are no randomized studies comparing various devices with nickel levels and device allergic reactions. In our study, we have attempted to gain insights into device-related nickel allergic reactions from a nonrandomized cohort who were clinically assessed for nickel allergy.

In our study, there were six patients with proven allergy to nickel who underwent interatrial shunt closure with the Helex device. None of these patients developed an allergic reaction to the device. None had any symptoms except for one patient who developed transient mild chest pain for one week after device implantation. There were trends toward a higher incidence of palpitations, atrial fibrillation, and chest pain in patients without nickel allergy treated predominantly with an Amplatzer device.

Rigatelli et al [12] described their experience with implantation of Amplatzer and Premere occluder devices in patients with a proven allergy to nickel. Within 24 to 48 hr of implant, eight of nine patients developed an "allergic device syndrome" presenting as concurrent chest discomfort, exertional dyspnea, asthenia, and mild leukocytosis. These symptoms lasted for a median duration of 11.5 days (range 8 to 42 days). All of them were treated with prednisone. In our study, none of the six patients with a nickel allergy treated with the Helex device then developed symptoms of an "allergic device syndrome." Comparing our six nickel allergic patients treated with Helex to the nine Rigatelli patients treated with Amplatzer or Premere, there is a statistically significant difference using the chi square test ($P < 0.001$).

There are several limitations to our study. We did not perform nickel skin testing for all patients. We

have obtained cutaneous patch test in only those with a suspected allergy to nickel. Second, we did not perform urine or blood testing to assess changes in serum or urine nickel concentrations after deployment of the interatrial shunt closure device. Though serum and urine nickel concentrations have been tested in a few studies [14,15], there is no gold standard method to measure nickel allergy after device implantation. Furthermore, it remains controversial whether cutaneous allergy to nickel correlates with intracardiac allergic response. Lastly, statistical comparison of our nickel allergic patients treated with the Helex device to Rigatelli's nickel allergic patients treated with either an Amplatzer or Premere device may be problematic if there were confounding factors. However, the inclusion criteria and definition for device allergic syndrome were similar between our studies.

In conclusion, our study shows that the Helex device appears to be a safe option in patients with a known allergy or hypersensitivity to nickel for percutaneous interatrial shunt closure. Future research is clearly needed to investigate the frequency of nickel allergic syndromes for contemporary devices used for interatrial shunt closure. It is important for blood and nickel testing data to be analyzed from ongoing randomized device trials. A randomized trial comparing different percutaneous inter-atrial shunt devices in patients with nickel allergy by skin testing is warranted.

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