

Nickel Allergy in Interatrial Shunt Device-based Closure Patients

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ABSTRACT

Background. The possibility of nickel toxicity has been raised with interatrial shunt closure devices constructed of nitinol. This study is aimed to assess the potential adverse symptoms in terms of incidence, duration, and significance, in patients with interatrial shunt and nickel allergy who underwent nitinol device-based closure.

Methods. We prospectively enrolled 46 consecutive patients (mean age 35 ± 28.8 years, 30 female) over a 12-month period referred to our center for catheter-based closure of interatrial shunts. Patients were investigated for previous hypersensitivity to nickel and were required to test potential nickel allergy with cutaneous patch test (TRUE test) before device implantation. Routinely, clinical visit with laboratory examinations, and TTE were scheduled at 1, 6, and 12 months.

Results. Nine patients (19.5%, mean age 31.3 ± 13.2 years) had proved symptomatic and instrumental nickel allergy as showed by cutaneous patch skin test but preferred to be implanted. All patients underwent successful transcatheter closure with an immediate occlusion rate of 100% without intraoperative complications. Between the 2nd and 3rd postoperative day, 8 out of 9 patients developed a sort of 'device syndrome' that included concurrent chest discomfort, exertional dyspnea and asthenia, and mild leukocytosis. The syndrome was treated with Prednison and Clopidogrel and in all was resolved after 1-week therapy. Interestingly, none of the patients without nickel allergy developed postclosure symptoms ($P < .001$).

Conclusions. In conclusion, nickel allergy is still a problematic issue in patients scheduled for transcatheter closure of intracardiac shunts; however, our brief study suggests that nickel allergy is not per se a contraindication to nitinol device closure.

Key Words. Congenital Heart Disease; Device; Allergy

Introduction

Nickel hypersensitivity occurs in up to 15% of the general population.¹ The possibility of nickel toxicity has been raised with interatrial shunt closure devices constructed of nitinol and in particular nickel allergy has been associated with generic side-effects in 2 patients,² with pericarditis in 1 patient,³ and with chest discomfort, palpitation, and increasing migraine headache in 4 patients.⁴ Despite such anecdotal reports, the mid-term follow-up of patients with nickel allergy implanted with intracardiac occluder device remains unclear. This study is aimed to assess on mid-term follow-up the results and potential adverse symptoms in terms of incidence, duration, and significance, in patients with interatrial shunt and nickel allergy implanted nitinol closure device.

Methods

We prospectively enrolled 46 consecutive patients (mean age 35 ± 28.8 years, 30 female, Table 1) over a 12-month period referred to our center for catheter-based closure of interatrial shunts: following our institutional protocol, all patients were screened with transesophageal echocardiography before the intervention. Patients were investigated for previous cutaneous hypersensitivity to nickel and were required to test potential nickel allergy with cutaneous patch test (TRUE test)⁵ before device implantation. Hypersensitive patients were informed about the possibility to experience adverse effects and were left free to choose alternative therapeutic options (surgery or drugs).

Inclusion criteria for atrial septal defect (ASD) closure included: Qp/Qs > 1.5 , enlargement of

Table 1. Demographic and Clinical Data of Enrolled Patients

Data	Mean $\pm$ SD or No. (%)
Age, y	35 $\pm$ 28.8
Male/female	16/30
Atrial septal defect	17 (36.9)
Mean right ventricle diameter, mm	49 $\pm$ 21.8
Mean Qp/Qs	2.4 $\pm$ 0.8
Mean pulmonary artery pressure, mm Hg	39 $\pm$ 11.3
Patent foramen ovale	29 (63.9)
Previous stroke	32 (69.5)
Migraine with aura	18 (39.1)
Migraine with no aura	2 (4.3)
Positive cerebral MRI	20 (43.4)
Transcranial Doppler shower pattern	23 (50.0)
Transcranial Doppler shower pattern	5 (10.9)
Platypnea orthodeoxia	4 (8.6)

MRI indicates magnetic resonance imaging.

right atrium (>16.84 mm area) and ventricle (inflow tract of right ventricle >35 mm)⁶, and ASD <40 mm. Indications for patent foramen ovale (PFO) closure included: shower or curtain pattern of shunt on transcranial Doppler⁷ with Valsalva maneuver, positive (single or multiple ischemic foci) cerebral magnetic resonance imaging, previous stroke or transient ischemic attack, medium or large PFO on transesophageal echocardiography.

All procedures were carried out under intracardiac echocardiography guidance using the mechanical 9F 9 MHz UltraICE catheter (EP Technologies, Boston Scientific Corporation, San Jose, Calif, USA) as previously described.⁸ Implanted devices were a full-nitinol device such as those of the Amplatzer Occluder family (PFO, Cribriform, ASD Occluder, AGA Medical Corporation, Golden Valley, Minn) and a low-nitinol device such as the Premere Closure System (St. Jude Medical Inc. GLMT, St. Paul, Minn). Aspirin 100 mg daily for 6 months was given routinely after device implantation.

Routinely, clinical visit was scheduled at 1, 6, and 12 months and included queries about the spectrum of symptoms after device implantation; transesophageal echocardiography was scheduled at 1 month and repeated at 6 months after closure if there was no more than a trivial shunt. Patients with PFO-related syndromes also underwent transcranial Doppler echography and magnetic resonance imaging of the brain before and 1 month after the procedure. Transthoracic echocardiography was scheduled at 6 months and 1 year after the transcatheter closure. Any residual shunt was graded as trivial, small, moderate, and severe as

previously described.⁹ Electrocardiogram-Holter monitoring was performed at 1 week and 1 month. Laboratory screening including hemoglobin value, leukocytes formula with eosinophilic count, erythrocytes sedimentation velocity, and reactive C protein was performed routinely before device implantation.

Statistical Analysis

Values are shown as mean $\pm$ standard deviation or percentages, whereas groups variables are compared by mean of χ^2 test or Student's *t*-test. Statistical level was set to value of $P < .05$.

Results

Nine patients (19.5%, mean age 31.3 ± 13.2 years) had proved symptomatic and instrumental nickel allergy as showed by cutaneous patch skin test and despite their allergy preferred to undergo to the device-based closure. All patients underwent successful transcatheter closure with an immediate occlusion rate of 100% in all patients without intraoperative or intrahospital complications. Eight out of 9 patients developed a sort of "device syndrome" that included concurrent chest discomfort, exertional dyspnea and asthenia in the absence of arrhythmias, instrumental pericarditis, pericardial effusion, device thrombosis, or femoral vascular complications. One patient developed only mild palpitation with normal EKG-Holter. Patients with "device syndrome" were almost all female (Table 2): symptoms arose early after the procedure (≤ 24 hours) in all patients. Six out of 8 patients suffered from migraine before the procedure: in 5 patients migraine completely disappeared after the procedure and in the mid-term follow-up. In 1 patient migraine worsened and ameliorated after the "device syndrome" disappeared. Hemoglobin and erythrocytes sedimentation velocity were normal in all patients as well as reactive C protein values that were within the normal range. Leukocytes formula demonstrated mild leukocytosis ($12.000 \pm 1540/\text{mm}^3$) with slight elevation of neutrophilic count. In 1 patient (the first one) the syndrome termed spontaneously after 5 weeks: symptoms have been judged aspecific and no therapy have been administered. After a collegial discussion when other patients presented the syndrome, we postulated a subclinical immunological response caused by nickel allergy and the syndrome was empirically treated in the other 7 patients (after 4, 7, 10, and 12 days after the procedure, respectively) with

Table 2. Summary of Clinical and Procedural Data of Patients with "Device Syndrome"

Patient	Gender	Device	Time to Symptoms	OC	Migraine Worsening after Closure	Therapy	Symptoms Duration*
1	Female	Amplatzer PFO 25 mm	2 d	No	Yes	No	5 wk
2	Female	Amplatzer ASD 22 mm	1 d	Yes	No	Yes	12 d
3	Male	Premere 25 mm PFO Occlusion	2 d	No	No	Yes	11 d
4	Female	Amplatzer ASD 20 mm	1 d	No	No	Yes	19 d
5	Female	Premere 25 mm PFO Occlusion	1 d	Yes	No	Yes	14 d
6	Female	Amplatzer Cribriform ASD 25 mm	2 d	Yes	No	Yes	10 d
7	Female	Amplatzer Cribriform ASD 25 mm	1 d	Yes	No	Yes	8 d
8	Female	Amplatzer PFO 25 mm	1 d	Yes	No	Yes	11 d

*Including the time passed from symptoms onset and start of the therapy.

ASD indicates atrial septal defect; ESV, erythrocytes sedimentation velocity; OC, Oral contraceptives; PFO, patent foramen ovale.

Table 3. Comparison between Patients with Nickel Allergy and Those Without

Data	Nickel Allergy N = 9	No Nickel Allergy N = 37	P
Age, mean $\pm$ SD	31.3 $\pm$ 13.2	35 $\pm$ 30	.87
Female, %	88.8 (8/9)	59.4 (22/37)	.09
ASD/PFO	55.5 (5/9)	32.4 (12/37)	.19
Qp/Qs	2.0 $\pm$ 0.3	1.9 $\pm$ 0.8	.78
Amplatzer device, %	77.7 (7/9)	78.3 (29/37)	.96
Premere device, %	22.2 (2/9)	21.6 (8/37)	.96
Complete closure, %	100 (9/9)	97.2 (36/37)	.61
Procedural complications, %	0 (0/9)	2.7* (1/37)	.61
Atrial fibrillation, %	0 (0/9)	5.4 (2/37)	.47
Leukocytes count, mean $\pm$ SD	12.000 $\pm$ 1540/mm ³	6.600 $\pm$ 3700/mm ³	<.01
Symptoms (any kind), %	100 (9/9)	5.4† (2/37)	<.001

*Pericardial effusion.

†Palpitations due to atrial fibrillation.

ASD indicates atrial septal defect; PFO, patent foramen ovale.

10 mg per day of prednisone and clopidogrel 75 mg per day (plus the usual dose of aspirin with the rationale of decreasing the inflammatory response and accelerating device endothelialization), until resolution of symptoms has been obtained, and in all was resolved after 1-week therapy. One patient observed worsening of migraine headache. Interestingly, none of the patients without nickel allergy developed postclosure symptoms similar to those of nickel allergy patients (Table 3): 2 patients had atrial fibrillation episodes that resolved with antiarrhythmic drugs. During the mid-term follow-up (30 ± 5.6 months), no recurrent paradoxical embolism or thrombus formation on the device surface was noted and all the patients did well without any other adverse symptoms.

Discussion

Current available devices are made of different materials: the Amplatzer (AGA Medical Corporation, Golden Valley, Minn, USA) is mainly made of nitinol, whereas Cardia Intrasept (Cardia Inc., Burnsville, Minn, USA), Premere (St. Jude

Medical Inc. GLMT), and others are made of tissue patch and a small amount of nitinol. Nitinol, a nickel-titanium alloy, is a valuable material in the construction of interventional endoluminal devices because of its biocompatibility, super elasticity, high resiliency, and shape memory. Although some authors reported no increase of concentrations of nickel in the blood of patients who have received Amplatzer nitinol devices,¹⁰ nickel seems to be released from the device, causing a systemic rise in serum levels of nickel, possibly until a calcium-phosphate layer has formed on the passive oxide film of the device or until endothelialization is complete.¹¹ Indeed, the normal healing process includes the initial deposition of fibrin and blood cells on the polyester fabric were subsequently organized by ingrown fibroblastic cells. Loosely arranged and poorly vascularized young granulation tissue is transformed time-dependently into quiescent fiber-rich connective repair tissue poor of cellular and capillary vessel components. Consistently, a mild chronic inflammatory response directed against textile fibers of both types of implants characterized by

lymphocytic infiltration and multinucleated foreign body giant cells.¹² Recently, Burian et al.¹³ observed that mean baseline concentrations of nickel in serum and urine in patients after Amplatzer Occluder implantation were within normal range with values of 0.6 ± 0.2 $\mu\text{g/L}$ and 3.1 ± 1.2 $\mu\text{g/L}$, respectively. In this study, nickel levels in serum increased up to 5-fold ($P < .01$ vs. baseline) during the 6-week postclosure period, the time needed for the formation of neointima on the surface of the graft. Moreover, the mean concentrations in serum and urine returned to baseline levels within 4–6 months post implantation. This evidence suggested that concentration of nickel in plasma and urine may be important in the healing process: this could be an issue also for hypersensitive patients, in whom an altered immunological response may be caused by nickel hypersensitivity particularly in the immediate postclosure status.

This temporal relationship could explain the significance of aspecific symptoms such as dyspnea, asthenia, palpitation, and chest discomfort observed in the first 2 weeks post implantation in our series. The occurrence of the so-called “device syndrome” both in patients with “heavy-nitinol” and “light-nitinol” devices may be explained with a mechanism “everything or nothing” related to allergic mechanisms. Gender would be an interesting factor: all but 1 patient were premenopausal female and almost all assumed oral contraceptives before the procedure. A certain impact of sex hormones on immunological response to device implantation may be an issue: hormones have been implicated to be related to stroke, headache in females with interatrial shunts^{14,15} and this would be important also after device implantation.

The apparent effectiveness of prednisone and increased therapy with antiplatelet agents to empirically treat this symptoms may be related to nickel plasmatic concentration and healing response: it seems to suggest that a subclinical immunological response, apparently confirmed by the mild leukocytosis, may be the most probable causes of this “device syndrome.”

Limitations of our study are related to the inability to objectively measure the presumed nickel allergy, the impossibility for ethical reasons to blind the subject to the results of nickel skin testing, and, for the same reasons, to randomly assign the patients to treatment or placebo.

In conclusion, although nickel allergy seems to have no impact in procedural and long-term results, nickel allergy is still a problematic issue in

patients scheduled for transcatheter closure of intracardiac shunts. New materials,¹⁶ and hopefully, reabsorbable materials, like the recent totally bioresorbable BioSTAR device,¹⁷ will make device closure of intracardiac shunts even more safe than today. However, our brief study suggests that nickel allergy is not per se a contraindications to nitinol device closure: side-effects are mild and simply manageable with low doses of prednisone and increased antiplatelet therapy.

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