

Positive Reactions to Nickel on a Patch Test Do Not Predict Clinical Outcome of Nickel Alloy-Based Atrial Septal Defect Occluder Implantation

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Key Words

Atrial septal defect closure · Nickel allergy · Nickel-titanium alloy device · Patch test

Abstract

Background: Patch testing is thought to be necessary prior to metal device implantation to rule out metal allergy-related complications; however, there are controversies over the effects of nickel allergy on the outcome of nickel alloy-based device implantation. **Objective:** This study aimed to evaluate the adverse events in a Korean population of nickel allergy patients who underwent atrial septal defect (ASD) closure with a nickel-titanium alloy-based device. **Methods:** We retrospectively reviewed the medical records of patients who underwent ASD closure with a nitinol device. **Results:** Among 38 patients who had ASD closure, 4 of 5 nickel-allergic patients and 10 of the 33 non-nickel-allergic patients had post-closure complications. All patients fared well, without device failure culminating in device removal. **Conclusion:** In this study, positive reactions to nickel in a patch test were not associated with adverse early or late outcomes following ASD closure with a nickel alloy-based device.

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Introduction

The use of implantable metal cardiac devices, including pacemakers, coronary stents and transcatheter septal occluders, has continuously been increasing. The currently available devices used to occlude atrial septal defect (ASD) are composed of different materials that include a distinct ratio of nickel. The Amplatzer device (AGA Medical Corporation, Golden Valley, Minn., USA) is an ASD occluder made of a nickel-titanium alloy, nitinol, which is composed of 55% nickel and 45% titanium [1]. The biocompatibility and shape memory of nitinol make this compound appropriate for the fabrication of endovascular and intracardiac devices [2]. Due to the presence of nickel in these implantable medical devices, potential complications from nickel allergy form the basis for controversy. Nickel hypersensitivity is one of the most common metal allergies and occurs in up to 15.5% of the general population [3]. Cutaneous contact with released metal ions induces a type IV hypersensitivity reaction mediated by allergen-specific T cells [4]. On the other hand, the possibility of immune-mediated toxicity by non-cutaneous implanted devices composed of nickel alloy remains to be elucidated.

The usefulness of a patch test to screen for potential deleterious outcomes has been disputed. In the field of orthopedics, metal orthopedic implants have been impli-

cated as the primary cause of allergies that may lead to implant failure. Kręcis et al. [5] insisted that patch test screening should be obligatory prior to implanting these devices into patients reporting symptoms of metal dermatitis and that patients with confirmed allergies to metals should be provided with implants without allergenic metals. Although anecdotal reports have chronicled side effects, such as pericarditis, chest discomfort, migraine headache and ASD occluder embolization leading to device removal after intracardiac device implantation [2, 6–8], some authors reported successful transcatheter closure even in patients with symptomatic nickel allergy, suggesting that nickel allergy per se is not a contraindication to ASD closure with a nitinol device; however, these contradictory results and concerns about the safety associated with long-term effects of implants underscore the value of post-implantation surveillance studies.

The aim of this study was to evaluate the outcome of ASD closure with a nickel-titanium alloy-based device in terms of prevalence and characteristics of potential adverse symptoms in patients with nickel allergy in the Korean population.

Patients and Methods

Patients

We retrospectively reviewed the medical records of all adult patients (age 20–60 years) who underwent ASD closure with the Amplatzer device from December 2011 to November 2012 in the Cardiology Clinic of Severance Hospital at Yonsei University. As a routine pre-implantation evaluation procedure, all patients were asked about previous hypersensitivity to nickel and other metals, and when metal allergy was clinically suspected, the patients were required to be tested for potential allergy using a cutaneous patch test before device implantation.

Patch Test

The patch tests were performed in the Allergy Clinic at the Department of Dermatology of Severance Hospital at Yonsei University. When metal allergies, including allergy to nickel, were confirmed by the patch test, the patients were informed about the possibility of adverse reactions, and a detailed explanation about other treatment options, such as surgery, was provided. With patients' consent, transcatheter ASD closure with the Amplatzer device was performed.

Evaluation of Clinical Outcome

Laboratory tests, including complete blood count with differential, acute-phase reactant, liver function and renal function tests were routinely performed before the implantation. Post-closure evaluations, including echocardiography and Holter electrocardiography monitoring, were performed. Aspirin (100 mg daily for 6 months) was routinely given after the closure. Adverse events of any kind during the follow-up period were evaluated.

Table 1. Epidemiologic data of patients who had ASD closure with the Amplatzer ASD occluder (n = 38)

	With nickel allergy (n = 5)	Without nickel allergy (n = 33)
Age, years	30.4±5.41	37.6±9.48
Female	5 (100%)	23 (69.7%)
Mean ASD size, mm	21.6±6.6	28.2±6.3

Data are presented as mean ± SD or n (%).

Table 2. Clinical outcome of ASD closure

	With nickel allergy (n = 5)	Without nickel allergy (n = 33)
Complete closure	5 (100%)	33 (100%)
Any adverse reactions	4 (80.0%)	10 (30.3%)
Chest tightness	1 (20.0%)	2 (6.0%)
Palpitation	0 (0%)	2 (6.0%)
Atrial fibrillation	0 (0%)	2 (6.0%)
Dyspnea	0 (0%)	3 (9.1%)
Migraine +/- aura	3 (60.0%)	5 (15.1%)
Leukocyte count	7,930±1,655.8	7,927.1±2,200.4
Eosinophil differential, %	1.9±1.6	1.4±1.0

Data are presented as mean ± SD or n (%).

Statistical Analysis

All data are shown as mean ± standard deviation or percentage, and group variables were compared by χ^2 test or Student's t test using GraphPad PRISM version 5.03 for Windows (GraphPad Software, San Diego, Calif., USA). Differences were considered statistically significant if the p value was <0.05.

Results

Between December 2011 and November 2012, a total of 38 adult patients (10 male, 28 female) had ASD closure (table 1). Seven patients were clinically suspected to have a history of metal allergy, and a cutaneous patch test was done by TRUE test [9]. Of these, five patients exhibited a positive reaction to nickel, while one patient had concomitant formaldehyde allergy. Among the patients without nickel allergy, one exhibited chromium allergy and another one had an allergic reaction to quinolone mix. In this study, following ASD closure with a nickel alloy-based device, both nickel-allergic patients and those without nickel allergy experienced adverse events (table 2). The characteristics of patients with symptomatic and

Table 3. Summary of clinical characteristics of patients with proven symptomatic nickel allergy

Case No.	Sex/age	Adverse event (onset)	Symptom duration	Therapy	Remark
1	F/38	nausea (POD 7)	1 week	no	
2	F/30	migraine without aura (POD 2)	continuous	yes	patch test: nickel, formaldehyde (+) status post kidney transplantation
3	F/27	intermittent migraine (previous migraine improved after closure)	6 months	no	thyroid cancer
4	F/33	chest discomfort (POD 1) migraine with aura (POD 30)	3 days 7 months	no yes	
5	F/24	no	NA	NA	

NA = Not applicable.

proven nickel allergy are shown in table 3. Interestingly, all five patients with nickel sensitivity were female.

Migraine was the most common complication observed in both groups and was the only adverse symptom that was significantly more prevalent in patients with nickel allergy than in patients without nickel allergy. Three of five nickel-allergic patients experienced migraine. On the other hand, five of 33 patients without nickel allergy experienced migraine. The onset of these migraines was between post-operative day 2 (POD 2) and POD 30 in patients with nickel allergy, and symptoms were controllable with aspirin or acetaminophen. Migraine subsided within the first year, except for one patient (case 2). In this individual, migraine headache without aura developed on POD 2 and persisted throughout the follow-up period (30 months). This patient exhibited a positive reaction for nickel and formaldehyde on the patch test. Furthermore, she also had been diagnosed with end-stage renal disease due to Henoch-Schönlein purpura and underwent kidney transplant after ASD closure. Her migraine headache was controllable with aspirin, but intermittent attacks were consistently present. The pre-existing migraine experienced by one patient (case 3) improved after ASD closure, although the patient experienced intermittent migraine attacks for another 6 months. She had previously undergone thyroidectomy for thyroid cancer and had been taking levothyroxine. Another patient (case 4) experienced migraine with aura for 7 months, beginning 1 month after the closure. The migraine improved after continuous anti-coagulant therapy with aspirin and clopidogrel. This patient experienced chest discomfort that also developed on the day following closure and lasted

3 days, but this symptom improved without treatment. In the patients without nickel allergy, five experienced migraine. Among these patients, two had pre-existing migraine, which improved within 1 year after the closure. Another patient experienced mild non-migraine headache, which began on POD 2, lasted for 3 months and was controlled without additional therapy.

Regarding chest discomfort, one patient with nickel allergy experienced chest tightness beginning on POD 1, and this symptom improved without treatment after 3 days. In addition, two of 33 patients without nickel allergy complained of chest discomfort and concomitant mild respiratory difficulty: one on the day following the procedure and the other within 2 weeks after the procedure. In these patients, close observation revealed that vital signs remained stable, and symptoms resolved without any treatment.

Some adverse symptoms, including palpitation, atrial fibrillation and dyspnea, were observed only in patients without nickel allergy. Palpitation and atrial fibrillation were each noted in two patients without nickel allergy, and dyspnea was observed in three patients without nickel allergy. With regard to atrial fibrillation, one patient had a personal and family history of chronic atrial fibrillation and experienced multiple recurrences even after the ASD closure. Defibrillation was necessary at every recurrence. Another patient had atrial fibrillation during the ASD device closure, but experienced no recurrence thereafter.

Nausea was noted only in one patient with nickel allergy. This patient (case 1) had mild nausea beginning on POD 7, but this symptom cleared without treatment within 1 week. The patients who exhibited quinolone mix

allergy and chromium allergy, but no nickel allergy, reported no adverse reactions during the follow-up period.

None of the in-hospital or short-term adverse events resulted in removal of the ASD closure device. A longer follow-up (24.1 ± 3.2 months) indicated no significant differences between the group with nickel allergy and the group without nickel allergy. Furthermore, all the patients fared well, and no additional new symptoms were noted during this longer follow-up period.

Post-procedure monitoring with echocardiography and Holter electrocardiography revealed successful ASD closure in all patients and no device failure. Laboratory test results, including leukocyte counts ($7,930 \pm 1,655.8$ vs. $7,927.1 \pm 2,200.4$) and eosinophil differentials (1.9 ± 1.6 vs. 1.4 ± 1.0) were not significantly different between the patients with nickel allergy and those without.

Discussion

Nickel is a ubiquitous metal used in a wide range of products, including those that may have prolonged contact with the skin (costume jewelry, zippers, cell phones, coins and keys). Although nickel is a common allergen in cutaneous hypersensitivity, the relevance of nickel allergy to the failure of cardiac devices via non-cutaneous contact remains unclear. With respect to post-ASD closure complications, Rigatelli et al. [1] defined 'device syndrome' as a constellation of symptoms, including concurrent chest discomfort, exertional dyspnea, instrumental pericarditis, device thrombosis and/or femoral vascular complications. The investigators reported that these symptoms arose in all patients with nickel allergy early after the procedure (within 24 h) and resolved after 1 week of therapy with aspirin, clopidogrel and prednisolone. Interestingly, no patients without nickel allergy developed post-closure symptoms similar to those of patients with nickel allergy. In another previous study of 47 patients who underwent patent foramen ovale closure with an Amplatzer device, eight patients were subsequently identified as having nickel allergy via patch testing at the time of follow-up [10]. Of these, five patients reported an increase in the frequency of migraine headaches, chest pain and palpitations after device placement, and this frequency was significantly higher than that reported by control subjects without nickel allergy. No differences in device performance were detected between the allergy group and the control subjects, and importantly, no evidence of implant failure was noted. On the other hand, in our study, both patients with nickel allergy and those without developed adverse events.

The patients without nickel allergy exhibited complications less frequently and with shorter duration. In addition, no aggravation of pre-existing migraine headache or chest palpitation was noted after the closure. Although migraine was significantly more prevalent in patients with nickel allergy, these symptoms were controllable with appropriate medications and mostly improved within several months. There were no statistically significant differences in incidence of adverse symptoms other than migraine headache, such as chest tightness, palpitation or dyspnea. Moreover, symptoms of palpitation, atrial fibrillation and dyspnea were more prevalent in patients without nickel allergy. All of the complications occurred within the first month post-closure and lasted no more than 1 year. Most importantly, no significant implant dysfunction leading to implant removal was observed.

Release of nickel ions from the device has been reported to be associated with plausible nickel-induced immune reaction in nickel-allergic patients [11, 12]. Although within normal limits, nickel levels in serum were reported to increase up to 5-fold during the 6-week post-closure period, and the mean concentrations of nickel in serum and urine returned to baseline levels within 4–6 months after implantation [13]. These results offer a possible reason for the occurrence of post-closure complications shortly after the procedure, mostly within the first month. Meanwhile, in a study assessing nickel release from metal alloys used in endovascular devices, nickel release was measurable from all alloys [12]; however, metal ion release from the studied stent alloys was not sufficient to activate expression of cellular adhesion molecules on endothelial surfaces or to induce cytotoxicity. Moreover, despite the high concentration of nickel in nitinol, this compound had the lowest nickel ion release of all studied alloys. These contradictory results suggest that nickel allergy may aggravate potential post-closure complications, but is not an essential factor for adverse reactions. Thus, although nickel ions are released from the device, it seems that the concentration of released nickel ions is trivial and may invoke mild adverse events, including migraine, in patients with a positive reaction to nickel on the patch test, but not sufficient to induce serious complications, such as device failure or generalized allergic contact dermatitis.

Interestingly, all five patients with nickel sensitivity in this study were female. Ear piercing at an early age has consistently been linked to the rise in nickel sensitization in recent years and may be responsible for the female predominance of nickel allergy. European regulations on the amount of nickel that may be released from objects with direct and prolonged skin contact, such as items inserted

into pierced body parts, have significantly reduced the incidence of nickel allergy among young Danish females from 27.6% in 1985 to 16.8% in 2007 [14–16]. Wet-work occupations and a greater exposure of women to high nickel content in jewelry may be precipitating factors, although other possibilities include sex hormone factors [15]. The true relationship between gender and nickel allergy-associated complications requires further study.

The limitations of our study stem from the fact that it was a retrospective analysis. Clinically symptomatic nickel-allergic patients were filtered by history taking and nickel allergy was confirmed by patch test; however, asymptomatic allergy may have been missed without patient awareness.

In the field of orthopedics, metal orthopedic implants are considered to be the primary cause of allergies that may lead to implant failure [4, 5, 17]. Patch test screening has increasingly been suggested to be obligatory prior to orthopedic metal implant insertion in patients reporting symptoms of metal dermatitis. In contrast, when it comes to intracardiac devices such as stents, foramen occluders and pacemakers, the relationship between metal allergy and device failure remains debatable [4]. In our study, positive reactions to nickel on the patch test were not related to adverse outcomes during early or late post-operative periods.

Importantly, no implant failure demanding implant removal was observed.

In conclusion, a patch test may serve as a valuable ancillary tool to confirm the delayed hypersensitivity reaction to nickel in the skin; however, positive reactions are not invariably relevant to complications and device failure, and negative reactions cannot rule out adverse events in the case of intracardiac device implantation. Therefore, when performing intracardiac implantation with nickel alloy-based devices, a patch test for nickel allergy does not appear to be necessary as a routine test, although such pre-procedural patch tests may predict mild complications such as migraine.

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Disclosure Statement

The authors have no conflict of interest to declare. There was no funding.

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