

Patch Testing for Metal Allergy With Manufacturer-Supplied Materials Before Nuss Bar Insertion

Kerry Heitmiller, BA, MSIII,* Andrea French, CRNP,† Samuel M. Alaish, MD,‡ Ronald Goldner, MD,* and Anthony A. Gaspari, MD*‡

Introduction: The increasing use of metal implantable devices has raised awareness of nickel allergy. Preoperative patch testing for patients with pectus excavatum (PE) with a known metal allergy or history of atopy is an accepted practice before the Nuss procedure. The Nuss bar manufacturer offers a metal disc for preoperative testing for metal sensitivities. However, the efficacy of this disc is not well understood.

Objective: The purpose of this study was to determine the sensitivity of the metal disc in detecting nickel allergy compared with that of standard patch testing.

Methods: Two PE patients were referred for preoperative patch testing with the metal disc to screen for metal allergy before the Nuss procedure. Based on our initial findings, 7 patients without PE scheduled for patch testing for the evaluation of chronic dermatitis were additionally tested with the metal disc if they were found to have risk factors for nickel allergy. All patch testing was performed according to set standards.

Conclusions: The metal disc may not be adequately sensitive to determine nickel allergy before the Nuss procedure. Patch testing alone with standard formulations of nickel sulfate in petrolatum may be more sensitive in diagnosing nickel allergy.

The increasing use of metal-containing medical implantable devices has raised awareness of nickel allergy. Most metal implants today are stainless steel and are made up of nickel, cobalt, and chromium. Numerous studies have related nickel allergy to various postoperative complications after metal implantation including dermatitis, chronic joint pain, edema, joint loosening, joint failure, in-stent restenosis, and even skin cancer.^{1–5}

The potential postoperative complications after metal implantation have led to an ongoing debate over the role of predictive patch testing that remains controversial. Recent studies have shown that, overall, up to 5% of patients experience cutaneous complications related to metal allergy after implantation,³ making this a clinically significant topic of interest. In the context of the Nuss procedure for patients with pectus excavatum (PE), preoperative patch testing for patients with a known metal allergy or history of atopy seems to be an accepted practice.^{6,7} The Nuss

procedure is a minimally invasive surgical procedure, during which a convex stainless steel bar, also known as the Nuss bar, is placed behind the sternum and left in place for approximately 2 years to allow for thoracic remodeling.^{8,9}

The Nuss bar manufacturer, Biomet Microfixation (Warsaw, Ind), now offers a metal disc to be purchased separately by the surgeon performing the Nuss bar insertion for preoperative assessment of metal sensitivity. The metal disc is manufactured to be a sample of the stainless steel Nuss bar so that tolerance to the Nuss bar can be evaluated. The stainless steel Nuss bar is composed of 17% to 19% chromium, 13% to 15% nickel, 2.2% to 3% molybdenum, and less than 2% manganese. On their Web site, Biomet Microfixation explains that the metal discs are “available for immunologists, dermatologist, or allergy specialists who wish to perform a scratch test, intradermal test, or blood test.”¹⁰ However, the manufacturer does not supply physicians with guidelines as to how to interpret results of testing with the metal disc, and studies evaluating the efficacy of the disc to detect metal sensitivity preoperatively are lacking. The study of Aneja et al¹¹ is the only other study that has evaluated the use of the metal disc. They concluded that it was not accurate in detecting metal allergy before the Nuss procedure after they found that patients determined to be negative for metal allergy based on preoperative testing with the metal disc developed clinically significant reactions after Nuss bar implantation.¹¹

From the Departments of *Dermatology, †Surgery, and ‡Microbiology/Immunology, University of Maryland School of Medicine, Baltimore, MD.

Address reprint requests to Kerry Heitmiller, BA, MSIII, Department of Dermatology, University of Maryland, c/o Dr Anthony Gaspari, 419 W Redwood St, Suite 160, Baltimore, MD 21201. E-mail: kerry.heimiller@som.umaryland.edu. The authors have no funding or conflicts of interest to declare.

DOI: 10.1097/DER.0000000000000149

© 2015 American Contact Dermatitis Society. All Rights Reserved.

TABLE 1. PE Patient Patch Test Results

Patient	Age, y/Sex	Risk Factors	Patch Test (48 h)		Patch Test (72 h)	
			Metal Disc	NiSO ₄	Metal Disc	NiSO ₄
1	16/female	None reported	Negative	Negative	Negative	Negative
2	14/male	Family history of nickel allergy; erythematous gingiva at area of contact with metal braces	Negative	1+	Negative	1+

Preliminary preoperative testing of 2 PE patients referred to our practice to assess metal sensitivity with patch testing to nickel sulfate and the metal disc revealed inconsistencies. Therefore, this led us to question the sensitivity of the metal disc in detecting metal allergy, specifically nickel contact dermatitis, preoperatively. We planned to determine the sensitivity of the disc in defining clinically relevant nickel allergy. Based on our preliminary findings, our hypothesis was that the metal disc provided for preoperative testing before the Nuss procedure is not sensitive enough to identify clinically relevant nickel allergy.

METHODS

In June 2014, 2 patients (1 male, 1 female) diagnosed with PE were referred by the University of Maryland Department of Surgery to the University of Maryland Dermatology Clinic for preoperative patch testing with the metal disc (supplied by Biomet Microfixation, Warsaw, Ind) to screen for metal allergy before the Nuss procedure. Patch testing was performed according to standards set by the North American Contact Dermatitis Group (NACDG).¹² Patients were patch tested with the standard NACDG tray, extended metal series (Chemotechnique), and the metal disc (Biomet). The patches were applied to the patient's back using Finn Chambers on Scanpor tape, and patches and the disc were kept in place for 48 hours. Reactions were scored at 48 and 72 hours based on the International Contact Dermatitis Research Group guidelines.^{13–15}

Before and after preoperative testing of the PE patients, a dimethylglyoxime (DMG) nickel spot test was performed on the metal disc to detect bioavailable nickel.^{16,17} Saline was applied before the application of the DMG solution. The metal disc was negative to the DMG test both before and after use of the metal disc

(no change in color was observed). A positive control (metal keys) was used to confirm the proper functioning of the DMG test to detect nickel with solid metal objects.

After preoperative testing of the PE patients, 7 patients (1 male, 6 female) without PE were scheduled for patch testing with the NACDG screening series (including NiSO₄) for the evaluation of chronic dermatitis. Patch testing occurred at the University of Maryland dermatology clinic between June 2014 and September 2014. Patients were additionally tested with the metal disc supplied by Biomet Microfixation if they were suspected to have nickel allergy. Nickel allergy was suspected if, upon history taking, the patients described pruritus and/or dermatitis upon wearing inexpensive or costume jewelry, or had risk factors for nickel allergy such as body piercings, history of atopy, family history of atopy or nickel allergy, or previous metal or dental implants.

Patch testing was performed according to standards set by the NACDG.¹² Patients were patch tested with the standard NACDG tray and the metal disc. The patches were applied to the patient's back using Finn Chambers on Scanpor tape, and patches and the disc were kept in place for 48 hours. Reactions were scored at 48 and 72 hours based on the International Contact Dermatitis Research Group guidelines.^{13–15}

RESULTS

The results of preoperative testing of the 2 PE patients are shown in Table 1. Patient 1 did not display any significant reactions to allergens on patch testing, and there was no reaction to the metal disc. Patient 2 displayed discordant results as there was a 1+ reaction to 2.5% nickel sulfate in petrolatum with a negative reaction

TABLE 2. Patient Patch Test Results at 72 h

Patient	Age, y/Sex	Risk Factors	Patch Test Results at 72 h			
			Nickel	Cobalt	Chromate	Metal Disc
1	44/female	Pierced ears; intolerance for inexpensive jewelry	2+	IR*	Negative	±†
2	56/female	Atopic; intolerance for inexpensive costume jewelry	2+	IR*	Negative	Negative
3	63/female	Pierced ears; intolerance for inexpensive costume jewelry; 2 stainless steel hip replacements	Negative	Negative	Negative	Negative
4	64/female	Pierced ears; intolerance/irritation with cheap earrings	±	Negative	Negative	Negative
5	48/female	Pierced ears; intolerance for costume jewelry	±	Negative	Negative	Negative
6	66/female	Hip replacements	Negative	Negative	Negative	Negative
7	33/male	Dental implant	2+	Negative	Negative	Negative

IR, irritant.

*Cobalt purpura.

†Only detected at 72 h.

to the metal disc. Patient 2 received a titanium Nuss bar instead of the standard stainless steel Nuss bar given the positive reaction to nickel on patch testing. Patient 1 received the standard stainless steel Nuss bar because no metal allergies were determined from preoperative testing.

To assess the sensitivity and accuracy of the metal disc in determining the presence of a nickel allergy, 7 patients in the dermatology clinic undergoing patch testing for prespecified reasons were also tested with the metal disc because they were suspected of having a nickel allergy. Based on patch testing, 5 (71.4%) of the 7 patients exhibited positive reactions to 2.5% nickel sulfate in petrolatum at 72 hours. Of these 5 patients, 4 patients (80%) did not exhibit reactions to the metal disc. The remaining patient (20%) showed only a weak $\pm$ reaction to the metal disc detected only at 72 hours after disc application. The 2 patients who did not exhibit reactions to nickel on patch testing also did not respond to the metal disc. Results are shown in Table 2.

DISCUSSION

The results of this study reveal inconsistencies between results of patch testing to nickel sulfate in petrolatum and the results of testing with the metal disc provided by the Nuss bar manufacturer. Four of the 5 patients who displayed positive reactions to 2.5% nickel sulfate in petrolatum on patch testing did not react to the metal disc. The 1 nickel allergic patient based on patch testing who also responded to the metal disc exhibited a weakly positive reaction to the metal disc in contrast to the strong reaction to nickel on patch testing. Therefore, similar to what was observed after preoperative testing of PE patient 2, the results of patch testing and the results of testing with the metal disc were discordant.

It is important to note that the patch testing schedule used in this study may have led us to miss some patients with positive reactions to nickel. Most patch test reactions occur at 72 and 96 hours.^{18,19} In our study, we scored reactions at 48 and 72 hours, thereby preventing identification of delayed positive reactions to nickel. Studies have shown that reactions to metals can become positive up to 168 hours after initial patch placement.^{18,20,21} In their study, Jonker and Bruynzeel²⁰ compared patch test readings at 48 and 72 hours with readings at 144 and 168 hours. They found that 8.2% of patients displayed late positive reactions at 144 or 168 hours to certain allergens including nickel sulfate.²⁰ Therefore, while it is possible that the patch testing schedule used in this study may not have allowed us to detect nickel allergy in those with delayed positive reactions to nickel, the patch testing schedule likely detected most nickel sensitive individuals, given that most positive reactions occur in the first 72 hours.^{18,19}

The inconsistencies between results of patch testing and testing with the metal disc can be partially explained by the differences in nickel bioavailability. There is a greater bioavailability of nickel in the 2.5% nickel sulfate in petrolatum used for patch testing compared with that of the metal disc. As mentioned in the Methods, a DMG test was performed on the metal disc before and after its use in

testing, and both times was found to be negative. This was surprising because the metal disc should contain nickel given that it is manufactured to be a sample of the stainless steel Nuss bar. Studies have estimated the detection limit of the DMG test to be the release of approximately $0.5 \mu\text{g Ni/cm}^2$ per week.^{22–25} Based on Danish and European Union regulations and confirmed by a number of studies, release of $0.5 \mu\text{g Ni/cm}^2$ per week is the level sufficient to elicit an ACD in a nickel sensitive individual.^{25,26} Therefore, the negative DMG test indicates that the disc likely releases less than $0.5 \mu\text{g Ni/cm}^2$ per week, which is insufficient to elicit an ACD reaction in a nickel sensitive individual. The nickel present in the metal disc may be more tightly bound preventing its release. In contrast, the 2.5% nickel sulfate in petrolatum has a nickel bioavailability of approximately $300 \mu\text{g Ni/cm}^2$ per day.²⁷ Therefore, the patch test is more likely to elicit an ACD in a nickel sensitive patient because it releases a sufficient amount of nickel. This would explain why the patients who exhibited strong reactions to nickel on patch testing displayed negative reactions to the metal disc.

It is possible, given the low bioavailability of nickel in the metal disc, that a contact time of 48 hours used in this study may not have been long enough to allow an adequate amount of nickel to be released from the disc and to elicit a contact allergy in the nickel sensitive patients. While a longer contact time may elicit an ACD reaction in more nickel sensitive patients, it would still pose a disadvantage of preoperative testing with the metal disc compared with patch testing. Preoperative testing with the metal disc would potentially take longer than with patch testing, which would likely be a greater inconvenience to the patient.

While the metal disc does not seem to be a sensitive method for detecting metal allergy when placed on the skin for 48 hours, it may be better used as an intradermal implant to study local hypersensitivity reactions. Given that the metal disc is composed of the same composition of metals as the stainless steel Nuss bar, implanting the disc may more appropriately evaluate its predictive value in determining metal allergy. In addition, the lower nickel bioavailability of the metal disc may become more significant in inducing a hypersensitivity reaction once implanted beneath the skin, and exposed to body fluids. However, this is an invasive technique that requires local surgery, and there are no guidelines for assessing allergy in response to metals implanted under the skin. Therefore, further investigative studies are needed to determine the appropriate procedural techniques, assessment of allergy in the setting of intradermal metal implants, and the clinical significance of the results of such a test.

Six- and 4-month follow-up of PE patient 1 and PE patient 2, respectively, revealed that both patients successfully underwent the Nuss procedure and are recovering well. Neither patient is reported to have any postoperative complications. It is important to remember that the decision for patient 2 to receive the titanium Nuss bar was based on the results of patch testing. The use of a titanium Nuss bar would not have been recommended if the metal disc alone had been used for preoperative assessment

of metal allergy. Preoperative testing with the metal disc alone did not detect nickel allergy in PE patient 2. The patient would have received the standard stainless steel Nuss bar, which may have led to postoperative complications.

The role of predictive patch testing in the setting of metal implantation remains a controversial and uncertain topic. Most dermatologists believe preoperative patch testing is only necessary for patients with a history of metal hypersensitivity reactions or for whom there is strong concern of a hypersensitivity reaction after implantation.^{28,29} Preoperative patch testing for patients without a known history of metal hypersensitivity is not considered to be necessary.²⁸ The value of preoperative patch testing has been assessed in the setting of dental, orthopedic, cardiac, and gynecological implants.²⁹ A history of hypersensitivity reactions to metals has been shown to be a predictor of positive patch test results to metals.¹ A study by Mesinkovska et al¹ 2012 demonstrated that when preimplantation patch testing results guided the choice of allergen-free orthopedic implants, those patients did not experience hypersensitivity complications after implantation. This study also showed that symptomatic patients patch tested after implantation with positive patch test results to a metal in their implant experienced resolution of postoperative symptoms after the implant was removed.¹ Therefore, these results support the use of patch testing before metal implantation among patients with a history of hypersensitivity reactions to metals and show the predictive value of the patch test in preventing after implantation hypersensitivity-associated complications.

The incidence of metal allergy among Nuss patients is estimated to be approximately 2.2%, although there is evidence that suggests this number may be as high as 6.4%.^{6,7} Shah et al⁷ 2014 reported a rise in after implantation metal hypersensitivity reactions despite preoperative patch testing those with a history of metal hypersensitivity. The study found that a family history of metal allergy and preoperative history of metal sensitivity correlated with metal allergy after implantation.⁷ Patients who did not report a history of hypersensitivity experienced after implantation hypersensitivity-related complications and were found to be metal allergic upon postoperative patch testing. This, therefore, suggests the value in broader preoperative patch testing for patients before Nuss bar implantation to prevent postoperative complications associated with metal allergy. Complications associated with metal allergy after Nuss bar implantation can manifest as an eczema and erythema of the anterior chest wall, inflammation and drainage at the incision site, persistent pleural effusion, and pericarditis.⁶ These reactions are clinically significant and can lead to significant pain, discomfort, and stress not only for the patient, but for the family as well. Based on our observational study, preoperative patch testing with nickel sulfate is a more sensitive method to determine metal sensitivity compared with the metal disc offered by Biomet Microfixation. This is important because the results of this study may contribute to the development of standards of the preoperative management of PE patients before the Nuss procedure. Individuals allergic to a component of a stainless steel Nuss

bar implant will typically receive a titanium Nuss bar instead of the standard stainless steel Nuss bar.⁶

There are a few limitations to this observational study. The main limitation is the nonrandomized nature of the study. Another limitation is the limited sample size. We evaluated a small cohort of nickel sensitive patients to assess the sensitivity of the metal disc in defining nickel allergy. Larger studies of nickel sensitive patients are needed to confirm these results.

CONCLUSIONS

We conclude that the metal disc offered by the Nuss bar manufacturer for preoperative assessment for metal allergy among PE patients is not adequately sensitive in screening for nickel allergy preoperatively. Patch testing with metals in petrolatum is a more sensitive and accurate preoperative method to test for nickel allergy. Guidelines for and studies assessing the use of manufacturer-supplied materials for preoperative testing in additional fields of medicine are needed to better understand the efficacy of these materials in defining metal allergy.

REFERENCES

1. Mesinkovska NA, Tellez A, Molina A, et al. The effect of patch testing on surgical practices and outcomes in orthopedic patients with metal implants. *Arch Dermatol* 2012;148(6):687–693.
2. Willert HG, Buchhorn GH, Fayyazi A, et al. Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study. *J Bone Joint Surg Am* 2005;87(1):28–36.
3. Niki Y, Matsumoto H, Otani T, et al. Screening for symptomatic metal sensitivity: a prospective study of 92 patients undergoing total knee arthroplasty. *Biomaterials* 2005;26(9):1019–1026.
4. Köster R, Vieluf D, Kiehn M, et al. Nickel and molybdenum contact allergies in patients with coronary in-stent restenosis. *Lancet* 2000;356:1895–1897.
5. Demehri S, Cunningham TJ, Hurst EA, et al. Chronic allergic contact dermatitis promotes skin cancer. *J Clin Invest* 2014;124(11):5037–5041.
6. Rushing GD, Goretsky MJ, Gustin T, et al. When it is not an infection: metal allergy after the Nuss procedure for repair of pectus excavatum. *J Pediatr Surg* 2007;42:93–97.
7. Shah B, Cohee A, Deyerle A, et al. High rates of metal allergy amongst Nuss procedure patients dictate broader pre-operative testing. *J Pediatr Surg* 2014;49:451–454.
8. Nuss D, Kelly RE. Congenital chest wall deformities. In: Ashcraft KW, Holcomb GW III, Murphy JR, eds. *Pediatric Surgery*. 5th ed. Philadelphia, PA: Saunders; 2010:249e65.
9. Nuss D. Minimally invasive surgical repair of pectus excavatum. *Semin Pediatr Surg* 2008;17:209–217.
10. Pectus Excavatum: Metal Sensitivity Overview. [Biomet Microfixation Web site]. Available at: <http://www.biomet.com/wps/portal/internet/Biomet/Healthcare-Professionals/products/microfixation/>. Accessed September 15, 2014.
11. Aneja S, Taylor JS, Soldes O, et al. Dermatitis in patients undergoing the Nuss procedure for correction of pectus excavatum. *Contact Dermatitis* 2011;65:317–321.
12. Zug KA, Warshaw EM, Fowler JF Jr, et al. Patch-test results of the North American Contact Dermatitis Group 2005–2006. *Dermatitis* 2009;20:149–160.

13. Fregert S. *Manual of Contact Dermatitis*. 2nd ed. Chicago, IL: Year Book Medical Publishers; 1981.
14. Wilkinson DS, Fregert S, Magnusson B, et al. Terminology of contact dermatitis. *Acta Derm Venereol* 1970;50:287–292.
15. Wahlberg JE. Patch testing. In: Rycroft, RJG, Menné, T, Frosch, PJ, Lepoittevin, JP, eds. *Textbook of Contact Dermatitis*. 3rd ed. Berlin, Germany: Springer; 2001:435–468.
16. Feigl F. *Test for Metals, Cations and Anions of Metallo Acids. Spot Tests in Inorganic Analysis*. Amsterdam, the Netherlands: Elsevier Science. 1958:149–153.
17. Gruvberger B, Bruze M, Fregert S, et al. Allergen exposure assessment. In: Frosch PJ, Menne T, Lepoittevin JP, eds. *Textbook of Contact Dermatitis*. Heidelberg, Germany: Springer. 2006:413–427.
18. Higgins E, Collins P. The relevance of 7-day patch test reading. *Dermatitis* 2013;24(5):237–240.
19. Beck M, Wilkinson S. Contact dermatitis: allergic. In: Burns T, Breathnach S, Cox N, et al, eds. *Rook's Textbook of Dermatology*. 8th ed. Oxford, United Kingdom: Wiley-Blackwell; 2010:26.84–26.90.
20. Jonker MJ, Bruynzeel DP. The outcome of an additional patch-test reading on days 6 or 7. *Contact Dermatitis* 2000;42(6):330–335.
21. Davis MD, Bhate K, Rohlinger AL, et al. Delayed patch test reading after 5 days: the Mayo clinic experience. *J Am Acad Dermatol* 2008;59(2):225–233.
22. Liden C, Rondell E, Skare L, et al. Nickel release from tools on the Swedish market. *Contact Dermatitis* 1998;39:127–131.
23. Lidén C, Norberg K. Nickel on the Swedish market. Follow up after implementation of the Nickel Directive. *Contact Dermatitis* 2005;52:29–35.
24. Menne T, Anderson KE, Kaaber K, et al. Evaluation of the dimethylglyoxime stick test for the detection of nickel. *Derm Beruf Umwelt* 1987;35(4):128–130.
25. Menne T, Bandrup F, Thestrup-Pedersen K, et al. Patch test reactivity to nickel alloys. *Contact Dermatitis* 1987;16(5):255–259.
26. Fischer LA, Menne T, Johansen JD. Dose per unit area—a study of elicitation of nickel allergy. *Contact Dermatitis* 2007;56(5):255–261.
27. Mendelow AY, Forsyth A, Florence AT, et al. Patch testing for nickel allergy: the influence of the vehicle on the response rate to topical nickel sulfate. *Contact Dermatitis* 1985;3:29–33.
28. Schalock PC, Thyssen JP. Metal hypersensitivity reactions to implants: opinions and practices of patch testing dermatologists. *Dermatitis* 2013; 24(6):313–320.
29. Schalock PC, Menné T, Johansen JD, et al. Hypersensitivity reactions to metallic implants—diagnostic algorithm and suggested patch test series for clinical use. *Contact Dermatitis* 2012;66:4–19.