

Nickel allergy: a reason for concern?

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INTRODUCTION

As the usage of intracranial stents continue to expand for wide-neck intracranial aneurysms, symptomatic intracranial atherosclerotic disease and other pathologies, an enigmatic problem that remains is in-stent stenosis (ISS). Most commonly, this phenomenon seems to take place as a result of neointimal proliferation. However, it has been postulated that the constituents of the metal alloys used in intracranial stents may also induce an inflammatory reaction that results in ISS. Thus, nickel ions, which are present in many of the metal alloys in intracranial stents, may cause a delayed-type hypersensitivity reaction leading to ISS. Studies examining the rate of ISS secondary to hypersensitivity reactions induced by nickel ion release in coronary stents have been equivocal. Based on the available data, we cannot conclude that prescreening for nickel sensitivity before the intracranial stent deployment is indicated, but further studies may be indicated, since the amount of nickel in coronary stents is far less than in the nitinol stents used in the cerebral circulation.

APPLICATIONS OF INTRACRANIAL STENT

The use of intracranial stents has expanded significantly over the past few years, especially with the advent of more flexible nitinol stents.¹ Intracranial stents have been shown to be an effective and safe method of revascularization in intracranial vessel disease secondary to atherosclerotic lesions and dissections.²⁻⁶ Many studies have shown greater efficacy in revascularization of intracranial stenoses than just angioplasty alone, as well as a decrease in rate of complications such as distal embolization and dissection.⁷

Additionally, the use of intracranial stents in the treatment of aneurysms has

grown dramatically. Studies as early as 1994 demonstrated the use of stents in the cerebrovascular circulation for dissecting aneurysms.⁵ In 1997, Higashida *et al* demonstrated the use of an intracranial stent as a scaffold through which coils were placed into an aneurysm in order to treat a fusiform basilar artery aneurysm.⁷ Stent-assisted coiling has now become a commonly used technique in the treatment of wide-necked or fusiform aneurysm in the intracranial circulation.^{1 8 9}

INCIDENCE OF STENOSIS WITH INTRACRANIAL STENTS

A significant problem with the use of intracranial stents has been the reported incidence of ISS. This is thought often to be secondary to neointimal hyperplasia,^{1 10 11} caused by smooth muscle proliferation and migration into the intima, leading to a fibrocellular neointima formation via an inflammatory response.¹² The SLYVIA trial, which examined the use of 316L stainless steel stents in the intracranial arteries, demonstrated a restenosis rate of 32.4% at the 6-month follow-up.³ The same study also showed a restenosis rate of 42.9% in extracranial vertebral stents at 6 months.³ Of the patients who developed >50% restenosis at 6 months, 39% had a symptomatic stroke between 30 days and 12 months after the initial stent placement. A linear regression model showed that the presence of diabetes, ostial stenosis location, postprocedural percentage stenosis, preprocedural vessel diameter, and age increased the risk of restenosis at 6 months.³ Another study specifically examined the Wingspan stent, designed for intracranial atheromatous disease, and found an in-stent restenosis rate of 29.7% after a mean follow-up of 6 months.¹³ In the treatment of cerebral aneurysms via Neuroform stents, Fiorella *et al* found the rate of delayed (>2 months) ISS to be 5.8%.¹⁴

The use of drug-eluting stents seems to have decreased the risk of restenosis, with one study showing an in-stent restenosis (>50% stenosis) rate of 6% after an average time of 4 months after initial

stent placement.¹⁵ Another study demonstrated no in-stent restenosis among eight patients treated with drug-eluting stents for intracranial atherosclerosis.¹⁶ The reduction in the rate of restenosis compared with bare metal stents has been attributed to the blocking of smooth muscle proliferation by sirolimus and paclitaxel, resulting in decreased formation of neointimal hyperplasia.

METALLIC COMPOSITION OF COMMON INTRACRANIAL STENTS

Most of the coronary stents comprise 316L stainless steel, which consist of approximately 12% nickel.¹⁷ It is with 316L coronary stents that studies have taken place to examine the association of nickel allergy with the development of in-stent restenosis. However, many of the intracranial stents consist of nitinol, an alloy that contains approximately 55% nickel and 45% titanium.¹⁷

Given the significant amount of nickel in these stents, it is possible that the inflammation derived from a delayed-type hypersensitivity reaction to the nickel may contribute to the process of neointimal proliferation and subsequent in-stent restenosis. Koster *et al* hypothesized that nickel ions may be eluted from the 316L stainless steel stents triggering an allergic response to the metal, and thus it is possible that the nickel ions eluted from a nitinol-based stent may lead to the inflammatory response resulting in new intimal formation around the stent.¹⁸

INCIDENCE OF RESTENOSIS OF CORONARY STENTS IN PATIENTS WITH NICKEL ALLERGY

Complications after implantation of coronary stents, such as in-stent restenosis, secondary to inflammatory processes, have been studied. It is known that in-stent restenosis after implantation of coronary bare metal stents is at least partially attributable to neointimal hyperplasia.¹⁷ It is estimated that the rate of in-stent restenosis after implantation of coronary stents is between 16 and 33%.¹⁷ There have been implications that the metal components of bare metal coronary stents, especially nickel, trigger a delayed-type hypersensitivity response leading to in-stent restenosis.

In a retrospective study by Koster *et al*, 131 patients with a bare metal stent (316L stainless steel), who were suspected to have restenosis, underwent repeat coronary angiography and patch testing for metal hypersensitivity.¹⁸ It was found

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that 10 patients had positive patch test results, and all 10 patients were found to have in-stent restenosis on repeat angiography (defined as >50% lumen loss). On the other hand, only 57% of the patients with negative patch test results had developed in-stent restenosis. However, this study did not examine the rate of metal allergy in patients without suspected restenosis, which may have led to a selection bias.¹⁹

However, another study by Hillen *et al* showed no significant association between the presence of a nickel allergy and the development of in-stent restenosis in coronary bare metal stents.²⁰ The study by Norgaz *et al*, which aimed to demonstrate the relationship between the presence of a nickel allergy and in-stent restenosis in a prospective study, also showed no significant association between in-stent restenosis and nickel allergy.²¹ In their study, three out of 43 patients with 316L stainless steel stents had a positive patch test response to nickel. Of these three only one was found to have in-stent restenosis on angiography. On the other hand, 15 out of 40 patients with a negative patch test reaction to nickel were found to have in-stent restenosis.

A retrospective study by Iijima *et al* showed that the development of recurrent in-stent restenosis may be associated with nickel allergy.²² One hundred and nine patients with initial stent deployment underwent coronary angiography in 6 months. The rate of positive patch tests in this group was not significantly different between patients with and without in-stent restenosis. However, an additional 65 patients were studied who had already undergone previous dilatation for in-stent restenosis. In this group, the rate of positive patch tests was 39% in those patients who were found to have recurrent in-stent restenosis versus 12% among those without recurrent stenosis.

ROLE OF DELAYED-TYPE HYPERSENSITIVITY WITH NEOINTIMAL PROLIFERATION

It is known that contact dermatitis to certain materials, including nickel, proceeds via a delayed-type hypersensitivity reaction, which is a cell-mediated reaction via CD4 lymphocytes. Naïve CD4 (TH0) cells are activated after presentation of an antigen and differentiate to TH1 or TH17 cells via cytokines released by antigen-presenting cells. Upon repeated exposure of the antigen, the previously activated TH1 cells release cytokines that activate macrophages,

resulting in the inflammatory response. TH17 cells, on the other hand, recruit monocytes and neutrophils.²³

Although the clinical manifestations of contact dermatitis are known to be secondary to the inflammation caused by the hypersensitivity reaction to the metal, it is not known whether a similar inflammatory reaction would take place around an endovascular device such as a stent. However, allergic reactions to metal ions have been seen in dental and orthopedic implants. A report by Thomas *et al* demonstrated a possible association of the loosening of an orthopedic implant with an allergic reaction to chromium ions.²⁴ The tissue around the implant showed an infiltration of oligoclonal T cells and expression of a TH1 cytokine profile.

Studies by Wataha *et al* have shown that nickel ions can promote or suppress the expression of intercellular adhesion molecule 1 (ICAM1) on the surface of endothelial cells, depending on the concentration of the nickel ions. These molecules are known to recruit inflammatory cells.²⁵⁻²⁶ Translating this to specific alloys used in stents, Messer *et al* studied the effect of exposure in vitro of endothelial cells to different metal alloys, including nitinol, CoCrNi, and NiCr.²⁷ The study showed that the amount of nickel ions released from the different alloys was significantly different. Interestingly, they showed that nitinol had the lowest amount of nickel ion release, despite having one of the highest concentrations of nickel. However, Messer showed that none of the alloys had sufficient nickel ion release in vitro to induce

expression of ICAM1 molecules on the endothelial cells. Moreover, none of the alloys were able to induce any significant amount of cytotoxicity to the endothelial cells, as measured by succinate dehydrogenase activity. On the other hand, exposure to nickel ions alone in concentrations >100 µmol/l resulted in a significant increase in expression of ICAM1 molecules on endothelial cells.

CONCLUSION

Based on available in vitro studies that examine the effect of nickel ions on endothelial cells, and on clinical studies examining the association of in-stent restenosis to inflammation induced by nickel in coronary stents, there does not seem to be overwhelming data to suggest a causal relationship between a hypersensitivity reaction induced by nickel-based intracranial stents and in-stent restenosis. Further studies, including randomized controlled trials, will be needed to establish or refute this relationship, particularly since many of the intracranial stents use nitinol, which has a much higher percentage of nickel composition, and has not been evaluated in the coronary or other arteries.

The question remains whether prescreening for nickel sensitivity in a patient is indicated before deployment of an intracranial stent. Honari *et al* recommended an evaluation algorithm for patients receiving an endovascular stent or cardiac device, consisting of a detailed history of previous contact sensitivity or reactions to common materials.¹⁷ This is followed by patch testing (figure 1) with an expanded North American standard screening tray



Figure 1 Vesicular reaction seen on nickel patch test with positive response.

Key messages

- No significant data exist to show a causal relationship between coronary artery restenosis following stenting in patients with nickel allergies.
- The percentage composition of nickel in nitinol cerebral artery stents is much higher than the percentage composition of nickel in stainless steel coronary stents.
- Data for the effect of nickel allergy in coronary stents cannot necessarily be extrapolated to nitinol cerebral stents.
- For patients with significant known nickel allergies, the decision to place an intracranial nitinol stent must be considered carefully.

(consisting of 65 common allergens) in those patients with a history of dermatitis or the abbreviated North American standard screening tray (consisting of 20 allergens) in those patients without a history of contact dermatitis. They also recommended testing with those constituents that are present in the device to be used.

Currently, there does not seem to be adequate data to justify prescreening for nickel allergies all patients who will receive an intracranial stent. Owing to the lack of study data on nitinol stents, however, we believe it is prudent to obtain a nickel patch test on patients who have documented or suspected nickel allergies, before elective nitinol stent placement, to provide better counselling for the patient and to consider treatment alternatives. Establishment of an association of nickel allergy with ISS in intracranial stents would justify this practice in the future. Should this association be established, further studies will be needed to quantify the role of prescreening in reducing the

incidence of restenosis after placement of intracranial stents.

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