

Preliminary Report of Serum Nickel Concentration After Atrial Septal Defect Occlusion with the Cocoon™ Device

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ABSTRACT

Background: The possibility of nickel release to the bloodstream after implantation of latest generation atrial septal defect occlusion devices (Cocoon Septal Occluder™), whose main component is nitinol (55% nickel and 45% titanium), remains controversial, especially in certain groups of patients such as children and women of childbearing age. Thus, the aim of this study was to evaluate the correlation between the device implantation and serum levels of nickel. **Methods:** This was a prospective longitudinal observational study conducted at a public hospital. Patients undergoing percutaneous atrial septal defect occlusion were clinically evaluated using transthoracic echocardiography and peripheral vein blood sampling for serum nickel before and after (1 day, 1 and 3 months) implantation. **Results:** The procedure and subsequent examinations were successfully performed in ten patients, with mean age of 34.4 years (range 5 to 60 years). Serial echocardiography confirmed the maintenance of adequate results of the procedure. Patients did not show manifestations that might suggest a reaction to metal, such as skin rash, dyspnea, thoracic discomfort, palpitations or migraine. Serum nickel levels did not show any significant changes and remained within the normal range for the population, according to the dosing methods within 3 months of the procedure. **Conclusions:** Preliminary results of this investigation with the Cocoon device have shown that during the initial period of endothelialization after the procedure there was no significant nickel release into the bloodstream.

DESCRIPTORS: Heart septal defects, atrial. Prostheses and implants. Metals. Nickel. Hypersensitivity.

RESUMO

Relato Preliminar sobre a Concentração Sanguínea de Níquel Após Oclusão Percutânea de Comunicação Interatrial com a Prótese Cocoon®

Introdução: A possibilidade de ocorrer liberação de níquel na corrente sanguínea após implante de dispositivos oclusores de comunicação interatrial de última geração (Cocoon Septal Occluder®), cujo principal componente é o nitinol (55% de níquel e 45% de titânio), ainda permanece controversa, principalmente em determinados grupos de pacientes, como crianças e mulheres em idade fértil. Dessa maneira, o objetivo do presente estudo foi avaliar a correlação entre o implante da prótese e os níveis séricos de níquel. **Métodos:** Estudo prospectivo de coorte, longitudinal e observacional, realizado em um hospital público. Pacientes submetidos à oclusão percutânea de comunicação interatrial foram avaliados clinicamente, por meio de ecocardiograma transtorácico, e foi feita coleta de amostras de sangue em veia periférica, para a dosagem do níquel antes e após (1 dia, 1 e 3 meses) o implante. **Resultados:** O procedimento e os exames subsequentes foram realizados com sucesso em dez pacientes, com média de idade de 34,4 anos (variação de 5 a 60 anos). O ecocardiograma seriado comprovou a manutenção dos resultados adequados do implante dos dispositivos. Os pacientes não apresentaram manifestações que pudessem sugerir reação ao metal, como rash cutâneo, dispneia, desconforto torácico, palpitações ou migrânea. Níveis séricos de níquel não apresentaram variação significativa e se mantiveram dentro dos limites de normalidade populacional dos métodos de dosagem até os 3 meses decorridos do procedimento. **Conclusões:** Os resultados preliminares desta investigação com a prótese Cocoon demonstraram que, durante o período inicial de endotelização após o procedimento, não ocorreu liberação apreciável de níquel para a corrente sanguínea.

DESCRIPTORIOS: Comunicação interatrial. Próteses e implantes. Metais. Níquel. Hipersensibilidade.

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The percutaneous closure of atrial septal defect (ASD) is the subject of constant research and development. Since it was first described in 1974,¹ as well as since the first Brazilian publication, in 1996,² double-disc stainless steel prostheses have predominated. The discs of these early models, which did not have a centralization mechanism, were one of the causes of their disuse, due to the difficult repositioning and handling of the prostheses.³

Most currently used devices consists of a nickel (55%) and titanium (45%) alloy,⁴ also known as nitinol (Nickel Titanium Naval Ordnance Laboratory), developed in the 1960s by the United States Navy.⁵ Nitinol has favorable physicochemical properties such as resistance to corrosion and material fatigue, thermal memory, and elasticity, which allow for the passage of large devices through small catheters, in addition to non-ferrous properties, which even allow the performance of MRI after implantation.^{4,5}

Considered a safe and effective alternative to conventional surgical atrioseptoplasty,^{4,6,7} such implants face new questions in the follow-up of a technique that has been under development for almost 40 years.

The main component of these prostheses, i.e., nickel, may be detectable in the bloodstream at higher levels than usual, which brings relevant implications regarding their biocompatibility.⁸ This is a non-existent problem in regard to stainless steel devices, which after implantation manifest a protective neointimal fibrous capsule that is up to 2 mm thick. Nitinol, in turn, produces a thinner neointimal response, which may be correlated to the oxidation of its superficial layer and the consequent release of metal ions into the bloodstream,⁵ which are therefore responsible for a higher serum concentration than that found in the general population. The latter, in theory, would be exposed to lower levels of nickel, introduced by water and food, and also through other routes, such as inhalation and even hemodialysis.^{9,10} In occupational exposure, there is inhalation of metallic dust and fumes containing relatively insoluble nickel compounds (nickel particulates), aerosols derived from nickel solutions, or gaseous forms (such as carbonyl nickel, for instance). The water-soluble forms are more easily absorbed, whereas the metallic form is the least absorbed.¹¹

Allergy after nitinol prosthesis implantation has been rarely described, with the development of skin rash,¹² as well as other symptoms such as dyspnea, pericarditis, chest discomfort, palpitations, and migraine with or without aura.^{3,4,13,14} These symptoms were more frequent in individuals that had a positive skin test reaction to nickel.¹⁵ More alarmingly, there are cases reports in which it was decided to explant the prosthesis without accurate or proven definition of the allergic reaction.¹⁴ The occurrences, although

rare, tend to manifest from 24 hours up to 6 weeks after device implantation.⁴

It is suspected that the severity of allergic reactions to nickel is directly proportional to the amount of nickel released into the bloodstream. In a randomized, double-blinded, placebo-controlled trial, in which a nickel solution was offered orally, it was documented that in the case of individuals who had previously shown nickel sensitization in skin tests, the longer the exposure, the higher the degree of skin manifestation.¹⁶ In a prospective study of 67 patients submitted to implantation of Amplatzer™ Septal Occluder devices (AGA Medical Corporation, Golden Valley, United States), an increase in serum nickel levels was documented, which reached its peak in the first month, without the occurrence of allergic manifestations.⁸

Multiple factors could influence the occurrence of clinical manifestations after prosthesis implantation, including nickel mass, the prosthesis surface exposed to the bloodstream, and the quality of nitinol wire used.¹⁵ In this context, latest-generation prostheses used to occlude atrial septal defects have been developed with coated nitinol wires.^{3,15} Therefore, they might present a distinct pattern of nickel release into the bloodstream. The present study, which is preliminary and pioneering, aimed to study this fact.

METHODS

Study design

This was a prospective cohort, longitudinal, observational study, performed at a single center, from August of 2013 to October of 2014, including 10 procedures from a total number of 20 patients undergoing percutaneous ASD occlusion using Cocoon Septal Occluder™ (Vascular Innovations Co. Ltd., Bangtanai, Thailand) prostheses. The study was performed at the Interventional Cardiology Laboratory of Hospital de Ribeirão Preto Medical School, Universidade de São Paulo, and was approved by the Research Ethics Committee of the institution (Opinion 174.986). All patients or their legal guardians, in case of underage patients, signed an informed consent after being notified of the study purposes.

Inclusion criteria

Individuals with ASD referred to Hospital das Clínicas with the following clinical, anatomical, and hemodynamic characteristics were included: weight > 25 kg; dilation of the right heart chambers visualized during echocardiography; QP/QS ratio > 1.5; mean pulmonary artery pressure ≤ 2/3 of the systemic level; pulmonary vascular resistance < 5 UW; defect diameter < 42 mm; and defect edges > 5 mm, unless they were retroaortic.

Exclusion Criteria

The exclusion criteria were: (1) a history of hypersensitivity or occupational exposure to nickel; (2) other congenital or acquired heart diseases, which had formal indication for surgical repair, as well as thin, hypermobile, or deficient septal defect edges; (3) active infection of any kind or infectious process in the previous month; or (4) hypercoagulability syndrome or contraindication to antiplatelet drugs.

One patient was withdrawn from the study, a prosthesis embolization into the left ventricle was observed approximately 24 hours after implantation, which required surgery to remove the device and ASD closure.

Outcome

This study assessed nickel release correlated with the implantation of the latest-generation atrial septal defect occlusion devices by serial nickel measurements in serum. The Cocoon Septal Occluder™ prostheses are manufactured using platinum-coated nitinol wire through a nano-fusion process. This characteristic could, in theory, result in a different behavior when compared to other devices previously submitted to similar assessment.

Follow-up

All ten patients were clinically evaluated through transthoracic echocardiography and collection of peripheral blood samples for nickel measurement before and after (1 day; 1 and 3 months) the implant, with protocol intention to repeat the measurement 6 months and one year after the implant. During the study, due to laboratory methodological reasons, the nickel measurement technique using atomic absorption spectrophotometry – graphite furnace – (normal < 4 mcg/L) was replaced

by mass spectrometry with inductively coupled plasma (normal < 7.5 mcg/L), which is more sensitive and can detect lower serum nickel levels with greater accuracy.¹⁷

During follow-up, patients were medically treated with acetylsalicylic acid at a single daily dose of 5 mg/kg (maximum dose of 100 mg/day) for 6 months. In adult patients, clopidogrel was associated at a dose of 75 mg/day for 3 months, with the intention to maintain it up to 6 months. Antibacterial prophylaxis was prescribed in case of surgical or interventional procedures, during the first 6 months of follow-up.

Statistical Analysis

Continuous variables were described with maximum and minimum values as well as means and standard deviations. Categorical variables were described as frequencies or percentages.

RESULTS

A total of ten patients, of whom six were women, were successfully submitted to the procedure. Age ranged from 5 to 60 years, with a mean of 34.4 years. Patient follow-up was 3 to 15 months (Table 1).

The implant was possible in all patients. Two patients had residual shunt at the transthoracic echocardiogram performed on the following day. After 30 days, minimal residual flow was observed in only one patient.

The patients had no clinical signs or manifestations that would suggest reaction to metal, such as skin rash, dyspnea, chest discomfort, palpitations, or migraine.

Measurement of the serum levels, due to the use of two different laboratory methods, is shown in absolute values (Table 2), as well as the ratio between nickel measurement/upper limit of the method's normality (Figure).

TABLE 1
Demographic, hemodynamic, and technical aspects of the atrial septal defect (ASD) occlusion procedure

Patients	Age (years)	Weight (kg)	Gender	ASD diameter (mm)	QP/QS	Prosthesis (mm)	Immediate residual flow	Residual flow after 30 days
1	49	100	M	31	NA	36	No	No
2	51	63	F	19	2.3	24	No	No
3	5	25	F	12	NA	14	No	No
4	60	55	F	20	NA	24	No	No
5	45	59.3	F	8	1.94	12	No	No
6	18	67	M	11	NA	14	No	No
7	35	50	F	14	NA	16	No	No
8	54	93	F	26	NA	32	Mild	Mild
9	12	57	M	16	NA	18	Mild	No
10	15	65	M	14	NA	16	No	No

Qp/Qs: pulmonary flow/systemic flow; M: male; NA: not assessed; F: female.

TABLE 2
Serum nickel levels (mcg/L)

Pre-implantation	1 Day	1 Month	3 Months
A: < 2	A < 2	B: 3.9	B: 7.6
A: 0.82	A: 1.04	Not collected	Not collected
A: 3.2	A: 3.1	A: 3.9	A: < 2
Hemolysis	Hemolysis	A: 1.9	A: 2.5
A: 2.4	A: 2.6	A: 1.3	A: < 2
B: 8.1	B: 6	B: 1.8	B: 0.8
B: 2.7	B: 3.4	B: 0.5	B: 1.3
B: 3.9	B: 4.1	B: 1	B: 1.8
B: 3.6	B: 4.6	B: 0.6	B: 0.8

A: atomic absorption spectrophotometry: normal < 4 mcg/L; B: mass spectrometry with inductively coupled plasma: normal < 7.5 mcg/L. In bold: slightly exceeding the upper limit of normality.

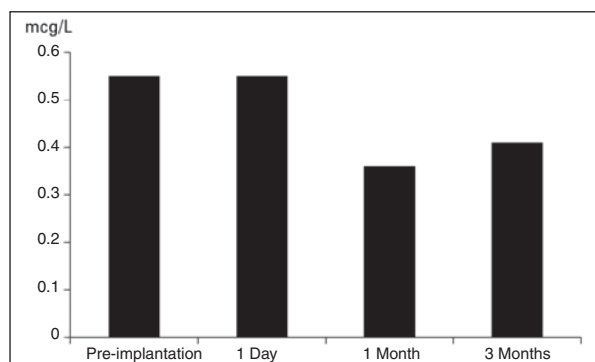


Figure – Means by period of association between nickel measurement and the method's upper limit of normality.

DISCUSSION

The development of nitinol has yielded undeniable progress, not only in cardiology but also in the incorporation to surgical resources in several procedures. Although its main component, nickel, is an essential element for nutrition in humans, implant devices that contain this metal deserve attention due to their toxic,^{8,11,18} allergic,^{9,15,18} and perhaps oncogenic and teratogenic potential.^{9,18}

Once the bloodstream is reached, 75%¹¹ of plasma nickel is carried by the circulating proteins, such as albumin and alpha-2 macroglobulin (called "nickel plasmin"). As the Ni²⁺ ions do not have a specific mechanism of uptake, they probably enter cells by Ca²⁺/Mg²⁺ channels. The main nickel elimination route is urinary, with the urinary excretion half-life ranging from 4.6 to 23 hours.¹¹ The measurement of urinary nickel levels is a currently used as a parameter of occupational safety control in some countries, but not by the national legislation. The regulatory standards that legislate and provide guidance on mandatory procedures

related to safety and occupational medicine, which are periodically reviewed by the Brazilian Ministry of Labor and Employment, included, in their 1978 version,¹¹ the reference values for the maximum allowed urinary nickel levels. In the latest version, from 1994,¹¹ there is no reference to the acceptable levels of urinary nickel.

Some of the adverse effects caused by the nickel occur due to its capacity to substitute essential elements such as manganese and to promote a possible effect of prolactin release.¹⁸ An *in vitro* genotoxic effect has also been described, acting in the S phase of the cell cycle, when there is heterochromatic DNA replication;¹⁸ however, there are conflicting data *in vivo*, in an attempt to define it as a carcinogenic or teratogenic factor, both in exposed workers and in experimental models.^{9,18}

The most important and prevalent health effects resulting from exposure to nickel is the allergic manifestation.^{9,15,18} A type IV hypersensitivity reaction (Gell and Coombs) develops, mainly caused by prolonged and repeated skin exposure to items such as clothing accessories (zippers, buttons, and decorations), clips, razor blades, cell phones, etc. It has a prevalence of 8-15%^{13,19} in the general population, which is even more pronounced in women – up to 17%.¹² Due to the higher prevalence of ASD in women, with proportions close to 2:1,²⁰ this population would be more often subject to exposure. Despite this fact, nickel exposure response through non-skin implants, as in ASD, still shows some uncertainties. For instance, studies have shown inflammatory activity with T-lymphocytes in peri-orthopedic implants in the hip of patients with a history of hypersensitivity skin reaction to metal, while other studies have shown conflicting results.¹⁹

A technological experimental study evaluated the behavior of 240 AmplatzerTM prostheses submitted to resistance testing with 400 million cycles, soaked in saline solution at 37°C for 14 months. After this period, the prostheses were evaluated through electron microscopy. There were no signs of microfractures or corrosion in the nitinol structures.⁵ This demonstrates that, regarding this model, the prosthesis has a low nickel release potential, even when submitted to extended wear under experimental conditions.⁵

In another study, which also used the AmplatzerTM prostheses, serum nickel levels were evaluated by atomic absorption spectrophotometry in 67 patients with ASD or patent foramen ovale (PFO).⁸ Blood samples were collected before and after implantation (1 day; 3 and 12 months). The following values were obtained, respectively, in ng/mL: 0.47; 1.27; 1.5; 1.24, and 0.25. These results suggest a transient increase, especially in the third month after implantation.⁸

In addition to the potential adverse effects discussed above, the possibility has been considered that, while the nickel serum levels were elevated, there was no

complete endothelial coverage of the device. Therefore, it would be plausible to maintain antiplatelet therapy while there is no normalization of serum nickel levels, which usually occurs within a period of 3 to 12 months.²¹

A histological study in ten nitinol devices, which had to be explanted from patients for several reasons, such as inadequate positioning or significant residual shunt in a period ranging from 5 days to 48 months after implantation, contributed to the understanding of so-called neoendothelization at the prosthesis implantation site.²² At the assessment by light microscopy and immunohistochemical panel, it was observed that the cell organization process initially forms fibrin deposits within a period of 5 days to 2 months and, subsequently, the differentiation occurs in cells with endothelial immunohistochemical characteristics. The endothelization would be complete 24 months after the implantation.²² Considering the results of this investigation, in which there was no increase in serum concentrations of nickel, it can be inferred that the nitinol strut coating prevented its release into the bloodstream. It could also be a sign of early endothelization, according to the experimental studies,^{5,8} a fact that would induce a shorter time of use of antiplatelet agents and antibacterial prophylaxis in the absence of residual shunt.

In the present sample, basal nickel values observed before the prosthesis implantation were higher than those found in literature.⁸ Considering this result, it is important to consider some factors. Regarding the laboratory method, atomic absorption spectrophotometry, it is known that this method is affected by several pathological conditions, such as myocardial infarction.²³ The assessment, at necropsies, of human myocardial tissues of previously healthy individuals that died from accidental causes has demonstrated that the heart is the preferred site of higher nickel deposition, when compared to other tissues.²³ It has been considered possible that the concomitant increase in albumin and nickel plasmin after the infarction could justify higher nickel concentrations. Other situations can also alter its serum levels, such as fractures, stroke, and burns.²³ Additionally, there may be aspects related to diet, including nickel-rich foods such as cocoa, cereals, and grains.¹¹

In the present study, it is noteworthy that serum alterations observed in nickel blood levels showed no direct correlation with the time of implantation. Thus, given the possibility that these results reflect fluctuations explained by the small sample size, the authors intend to pursue the inclusion of patients in this study, as well as to complete the follow-up with additional collections for up to one year of prosthesis implantation.

In agreement with a recent publication by Chamié et al.³ regarding the two new coated nitinol mesh prostheses, about which there are few references in the literature and that have been implanted in 49 patients (Lifetech CERA™ ASD Occluder and Cocoon

Septal Occluder™), it was observed that the handling and the functional profile of the devices used are very satisfactory. More studies and a long-term follow-up are needed to document some aspects related to the potential benefits of coated nitinol wires, which in addition to increasing the device radiopacity, facilitating its visualization and its positioning under fluoroscopy, appear, considering the results of this investigation, to promote the effects of reduced nickel release into the bloodstream and increased occluder biocompatibility.³

CONCLUSIONS

The preliminary results of this investigation with the Cocoon™ prosthesis showed that, during the initial period of endothelization after the procedure, there was no significant release of nickel into the bloodstream.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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None declared.

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