

Blood nickel level and its toxic effect after transcatheter closure of persistent duct arteriosus using Amplatzer duct occluder

Mulyadi M. Djer, Bambang Madiyono, Sudigdo Sastroasmoro

Abstract

Background Transcatheter closure using amplatzer duct occluder (ADO) is currently the treatment of choice for patent ductus arteriosus (PDA). The ADO device is constructed from a Nitinol wire mesh containing 55% nickel. Up to now, there is still a controversy about the effects of nickel contained in ADO.

Objectives To determine blood nickel level at six months after transcatheter closure of PDA using ADO, toxic effects of nickel at six months after PDA closure using ADO, and the effects of nickel on complete blood count (CBC), blood glucose and renal function.

Methods Subjects were patients with PDA at Integrated Cardiovascular Services, Dr. Cipto Mangunkusumo Hospital, Jakarta. Routine blood test and blood nickel levels were measured at the time of the procedure, and at the end of the first, third, and sixth months after intervention.

Results There were 29 patients who underwent heart catheterization and PDA closure using ADO. A time series analysis was conducted on 23 patients who completed six-month follow-up after the intervention. Median blood nickel level before procedure was 58 ng/mL while at one, three and six months afterwards were 60, 63 and 64 ng/mL respectively. The blood nickel levels did not differ significantly between pre- and post-ADO. After PDA closure, no toxic effects of nickel were found, both clinically and laboratorically.

Conclusions PDA closure using ADO has no effects on the nickel levels, CBC, blood glucose and renal function; [Paediatr Indones. 2009;49:33-8].

Keywords: patent ductus arteriosus, amplatzer duct occluder, nickel, nitinol, inductively coupled plasma spectrometry

Transcatheter closure is currently assumed to be the treatment of choice for patent ductus arteriosus (PDA). This procedure has been continuously developing in the last 10 years.¹⁻⁵ amplatzer duct occluder (ADO) is the only available device used to close PDA which has been recommended by US Food and Drugs Administration. It is made from a Nitinol wire mesh which contains 55% nickel.⁶ Up to now, there is still a controversy about the effects of nickel contained in ADO especially whether it is released to the blood and its side effects.⁷⁻¹⁰

Particular concerns about nickel intoxication in human arised from a report stating a high rate of intoxication and cancer in nickel factory workers caused by inhaling this particle. One study also reported nickel intoxication in people who ate or drank nickel containing food or food that is cooked using nickel containing tools. Whether devices

From the Child Health Department, Medical School, University of Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Reprint request to: Mulyadi M. Djer, MD, Department of Child Health, Medical School, University of Indonesia, Cipto Mangunkusumo Hospital, Jl. Salemba 6, Jakarta 10430, Indonesia. Tel. 62-21-3907742. Fax. 62-21-3907743.

placed into the heart and blood vessels would have the same toxic effects as inhaled or digested nickel is still controversial. In patients with atrial septal defect (ASD) closed by Amplatzer Septal Occluder (ASO), Ries *et al*¹¹ found that nickel is released to the blood from this device, causing systemic rise in blood nickel levels. In contrast, Coe *et al*¹² reported that there was no blood nickel level increase post-ASD closure using ASO. On the other hand, there was a case report about the occurrence of pericarditis after ASD closure using ASO, assumed to be an allergic reaction to nickel.¹³ A study about the effects of nickel in PDA patients has never been performed.

The purposes of this study were to determine blood nickel level as well as the clinical as well as laboratory toxic effects of nickel at six months after PDA closure using ADO.

Methods

This was a prospective interventional study using single factor design for repeated measurements for PDA patients undergoing transcatheter closure using ADO. The study was conducted at Integrated Cardiovascular Services in Dr. Cipto Mangunkusumo Hospital, Jakarta from November 2006 to February 2008. This study was approved by Ethics Committee Faculty of Medicine University of Indonesia.

Patients were suspected to have nickel intoxication if they have one or more signs and symptoms of nickel intoxication such as persistent headache, vomiting, increased work of breathing, stomach ache, diarrhea and dermatitis without other explainable causes and laboratory examination revealing increased blood nickel level above baseline level.

To measure the toxic effect of nickel on some organs, we examined complete blood count, i.e., hemoglobin, white blood cell (WBC), hematocrit, and platelets as well as blood glucose, blood urea nitrogen (BUN), creatinin, and glomerular filtration rate (GFR) using Schwartz method. Laboratory examination was done at Prodia Laboratory, Jakarta. Blood nickel concentration was measured by inductively coupled plasma (ICP) spectrometry with the IRIS Intrepid II XDL Extreme Detection Limits Inductively Couple Plasma Spectrometer at Regional Health Laboratory of Jakarta.

All measurements were done four times, i.e, before intervention, and at one, three, and six months afterward. A time series/repeated measures Anova test was applied for numeric variables with normal distribution. If the distribution of numerical variable was not normal, it was transformed into using logarithmic scale. If the distribution of the log-transformed variables was normal result, time series analysis was applied, but if the results was not normal, Friedman test was used. Cochran test was applied for nominal scale.

Sample size was calculated using paired two group formula plus 10% possibility of subject drop-out. According to the above formula, the minimal subject required was 23 children.

Results

This study was conducted since November 2006 until February 2008. During the period, there were 29 patients undergoing transcatheter closure of PDA using ADO at the Cardiovascular Intergrated Services, Dr. Cipto Mangunkusumo Hospital, Jakarta who were recruited in this study. Subjects' age ranged between 5 months and 14 years, with 23 months as the median age. The number of girls (17) outweighed boys (12). Body weight ranged from 6.6 kg to 55.0 kg with median of 11.0 kg. Body height or length ranged from 65 to 162 cm with median of 82 cm. Body surface area (BSA) ranged from 0.35 m² to 1.6 m² with median of 0.47 m². The data of hemodynamic measurements, size of PDA, size of device used and hospital stay are shown on **Table 1**.

Blood nickel level

In this study, there were 23 subjects included into the time series analysis who had completed six-month follow-up. **Figure 1** shows the change of blood nickel levels before and at one month, three months and six months following implantation of ADO. The median blood nickel level before procedure (baseline) was 58 ng/mL. One month after the procedure, it increased to 60 ng/mL, which was statistically not significant (P=0.760). Three months and six months after the procedure, blood nickel level increased to 63 ng/mL (P=0.790) and 64 ng/mL (P=0.152), respectively.

Table 1. Results of catheterization and intervention (n=29)

Variable	Mean	SD
PA/Ao ratio	0.5	0.19
Flow ratio (Qp/Qs)	1.8	0.7-6.3
PDA size (mm)	3.4	2.1-10.3
ADO size (mm)	6	4-14
Fluoroscopy time (minute)	16	6-92
Procedure time (minute)	66	42-148
Hospital stay (day)	1	1-2

Note: SD=Standard deviation; PA=Pulmonary artery; Ao=Aorta; Qp=Pulmonary blood flow; Qs=Systemic blood flow; PDA=Patent ductus arteriosus; ADO=Amplatzer duct occluder.

Signs and symptoms of the toxic effect of nickel

To determine whether nickel contained in ADO could cause toxic effect, the patient was monitored regularly. In this study the signs and symptoms of nickel toxic effect due to nickel contained in ADO which was implanted into the heart and blood vessel were evaluated. During six-month follow-up, there were no signs and symptoms of the toxic effect found.

The effect of nickel towards laboratory parameters

We examined the direct effect of PDA closure itself as well as the toxic effect of nickel contained in ADO towards some of complete blood count components, including hemoglobin level, hematocrit, WBC, and platelet count.

Patients hemoglobin level increased significantly from 10.9 g/dL before PDA closure using ADO to 12.8

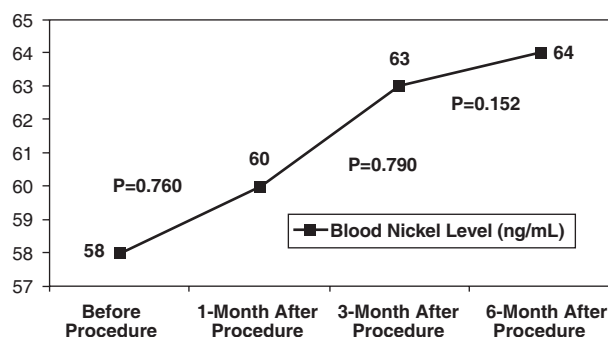


Figure 1. Blood nickel level before procedure and at one month, three months and six months after the procedure.

g/dL ($P < 0.0001$). Hemoglobin level kept increasing to 12.9 g/dL on three-month follow-up and to 13.0 g/dL on six-month follow-up after the procedure, although they were not statistically significant ($P = 0.885$ and $P = 0.858$). At one-month observation after ADO procedure, hematocrit level increased significantly from 32 vol% to 37 vol% ($P < 0.0001$). At three months follow-up, the hematocrit level tended to be stable, while at six-month follow-up, the hematocrit continued to increase to 38 vol%, although this was not statistically significant ($P = 0.459$). Data are shown on **Figure 2**.

As the hemoglobin and the hematocrit level, WBC count also increased significantly from 8,398/ μ L before the procedure to 11,304/ μ L afterward ($P < 0.0001$). There was a slight decrement in WBC count at three-month follow-up, but at six-month follow-up the WBC count continued to increase, even though this differences were not statistically significant. The platelet count before PDA closure was 106,666 / μ L. In contrary to hemoglobin, hematocrit, and WBC count, there was only slight increment in platelet level at six-month of follow-up and this was not statistically significant.

In order to observe the toxic effect of nickel on vital organs, we also performed serial examination on several laboratory parameters which were blood glucose level, BUN, creatinine, and GFR using Schwartz method.

The median blood glucose level before ADO procedure was 149 mg/dL which was higher than normal. At one-month after PDA closure, blood glucose level decreased significantly to 88 mg/dL (P

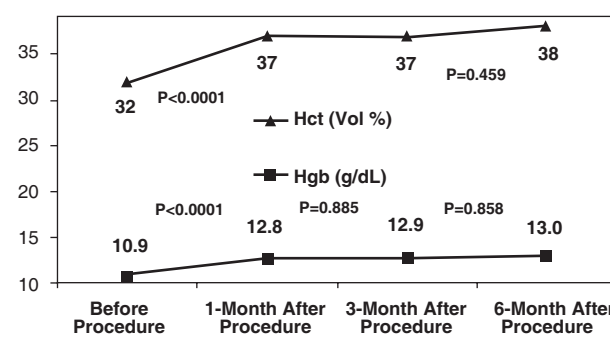


Figure 2. The changes of hemoglobin and hematocrit before and at one-, three- and six-month after procedure.

<0.0001), while at the next observation (three-month after the procedure), it decreased slightly before rose again thereafter. Differences in blood glucose level after one-month of ADO procedure was not statistically significant.

The BUN before the procedure was 21.5 mg/dL. There were no significant differences among BUN level before and on one-, three-, and six-month after the procedure ($P=0.080$). Similar to BUN, there were also no significant differences between creatinine levels before the procedure and at one-, three-, six- months afterwards. GFR was determined using the Schwartz methods based on the level of blood creatinine and body surface area. Before the procedure, the median GFR was 198 mL/min/1.73 m². There was no a statistically different in levels of GFR before and at one-, three-, six- month after the procedure.

Discussion

In this study, ADO was successfully implanted in all patients. During the procedure, there were no complications occurred. After the intervention, no patient was admitted to the ICU and most were discharged one day after. The results of this study were similar with some previous reports.²⁻⁵

The issue of the toxic effects of nickel was emerged due to reports of the inhaled nickel in employees working on factories that dealt with nickel. Trombetta *et al*⁸ reported the toxic effect of nickel on several organs, especially the respiratory tract epitels. Young *et al*⁷ also reported the toxic effect of nickel on some organs in human body. Zoruddu *et al*¹⁰ and Costa *et al*⁹ reported that the carcinogenic effects of nickel were associated with epigenetic through histone H4 protein. Most reports showed the adverse effects of nickel that entered the body through the inhalation route.⁷⁻¹⁰ However, Young⁷ reported cases of nickel toxicity after ingestion of foods containing high level of nickel. Besides that, there was also a report of nickel toxicity due to ingestion of foods and drinks that were prepared using nickel-made cookwares.

Recently, plenty of medical devices using nickel are implanted to the human body.^{5,6} Usually those are made from alloys consisted of 55% nickel and

45% titanium. This alloy is named Nitinol (Nickel Titanium Naval Ordnance Laboratory). Nitinol wire is very elastic, durable and free of electromagnetic field.⁶ Examples of medical devices made from nickel are pacemaker, stent, Amplatzer device for the management congenital heart disease, tooth wire, and orthopedic fixation device implanted to the bone.⁶ Whether the nickel implanted in the human body has the same effects as inhaled nickel is still under investigation. On the other hand, there were also some cases of skin allergic reaction to jewelries containing nickel.

Our study demonstrated that the blood nickel level observed on six-month follow-up after the ADO procedure did not increased significantly. This data was contradictory to those of Ries *et al*¹² who reported that nickel contained in devices used to close ASD was released to the blood stream and caused significant elevation of blood nickel level compared to the level before the procedure. However, the results of our study confirmed those of Coe *et al*¹¹ who stated that there were no differences in blood nickel level before and after the procedure. Ries *et al*¹² reported that the risk of nickel released to blood stream occurred within six months after the intervention before the device was covered by thrombus formation. Thrombus formed in static flow areas (venous) was different in timing, composition, and characteristics from those formed in rapid flow areas (arteries). Thrombus formed faster in cardiac chamber with slow blood flow, but with more fragility due to higher red blood cell content (red thrombus). On the other hand, thrombus formation in high flow areas takes more time and contains more fibrins (white thrombus), make it more durable.¹⁴ Therefore, Amplatzer devices for PDA and ASD closure have distinguished effects on the blood circulation because of the different implantation sites. Our findings showed that the concern of nickel released to the blood stream was not proven.

Laboratory values are helpful tools to assess the consequences of PDA closure and the side effects of nickel, a component of Amplatzer device. Changes in laboratory values can also depict clinical improvement, e.g. increased appetite, good organ perfusion due to improved cardiac output, and reduced catabolism from less frequent respiratory tract infection after PDA closure.

Hemoglobin level is an important parameter to monitor treatment results. Many factors influence the hemoglobin level. In this study, hemoglobin changes could be an indirect effect of PDA closure and also can be a direct effect of nickel toxicity causing anemia or hemolysis as a mechanical consequence of the device itself.¹⁵ This study showed that there was a significant increase in post-PDA closure hemoglobin level from 10.9 g/dL to 12.8 g/dL ($P < 0.0001$). These incremental changes may be indirectly caused by PDA closure resulting in clinical improvement and better organ perfusion due to better cardiac performance. These resulted in better appetite and less frequent respiratory tract infection, which gave rise to the hemoglobin level. On three and six-month follow-up after the procedure, there was still a statistically insignificant increase in hemoglobin level. The consistent rise in hemoglobin level ruled out the assumption of nickel toxicity.

Changes in hematocrit level were consistent with the hemoglobin level. In this study, there was significant increase of hematocrit level one month after PDA closure, from 32 vol% to 37 vol% ($P < 0.0001$). After that, in three-month and six-month follow-up, the hematocrit level still increase insignificantly. Both hematocrit and hemoglobin increments were resulted from indirect effect of PDA closure. Consequently, the patient's condition improved, along with better organ perfusion due to better cardiac performance. Decremental changes of hematocrit due to fluid retention from nickel were not demonstrated in this study.

Animal experimental study showed that nickel could suppress white blood cell count.⁷ However in our study, there were no decremental changes in white blood cell count. After ADO procedure, the white blood cell level increased significantly from 8,398 μL to 11,304 μL ($P < 0.0001$). Apparently the elevation of the white blood cell count was caused by nonspecific body reaction to foreign bodies. Sometimes, the presence of foreign body caused mild fever without changes in other parameter of infection.² At three-month of follow-up, there was a slight decrease in white blood cell count, followed by another increment, albeit insignificant.

One of the toxic effects of nickel is the decrease of platelet count.⁷ This study showed that the platelet count within six months after PDA closure with ADO did not change significantly, suggesting that

the nickel in the Amplatzer device did not affect platelet counts. According to Watts¹⁶ nickel could influence insulin receptor in the tissue which would cause hypoglycemia through prolongation in insulin activity. In our study, blood glucose level before PDA closure was higher than that of normal values. The reason might be that the first blood sampling was taken during the intervention while the patient had already been under dextrose infusion. Therefore subsequent blood glucose level taken one month after the ADO procedure returned to normal values and was sustained until the end of the six-month follow-up. The dramatic decreasing of blood glucose level at one-month follow up might due to dextrose infusion discontinued rather than nickel toxicity. This was supported by the stable blood glucose levels until six months after the procedure. Thus nickel toxicity on blood glucose level was not confirmed in this study.

There were little changes in BUN level before and after the PDA closure, while creatinine level increased from 0.2 to 0.3 mg/dL at three-month after the ADO procedure, which was still within the normal range. The GFR according to Schwartz did not differ significantly before and after the procedure. According to Young *et al*⁷ the kidney was one of the target organs of nickel toxicity, but this study did not show disturbance in renal function caused by nickel from the Amplatzer device.

We concluded that after PDA closure using ADO, there are neither increase of blood nickel level nor sign or symptom of nickel intoxication. Nickel contained in ADO has no effect on complete blood count, blood glucose and renal function.

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