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Comparison of trace element levels after cardiopulmonary bypass between cyanotic and acyanotic patients*

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Abstract

Trace elements are essential micronutrients for the human body. In this study, we evaluated the alterations in copper, chromium, manganese, selenium, magnesium, zinc, iron, arsenic, boron, and silicon levels in children with cyanotic and acyanotic CHD who underwent cardiac surgery with cardiopulmonary bypass. Participants were divided into the following three groups: patients acyanotic CHDs (n = 34), patients with cyanotic CHDs (n = 30), and healthy controls (n = 30). Blood samples were collected before the surgery and 1 hour after the sternum was closed. Serum trace elements were determined by Inductively Coupled Plasma Optical Emission Spectrometer-ICAP 6000. The baseline serum arsenic, manganese, and zinc levels of both patient groups were lower compared with controls, but there was no significant difference between baseline serum trace element levels of cyanotic and acyanotic patients. In both the patient groups, there was a significant decrease in postoperative serum arsenic, boron, copper, and zinc levels, and a significant increase in postoperative serum iron and magnesium levels. Silicon levels increased in cyanotic patients. Alterations in trace element levels were in the same direction in cyanotic and acyanotic patients. Copper, zinc, and manganase replacement may be needed after on-pump cardiac surgery.

Chemical elements present in very small quantities (<0.01% of the body weight) in the body are termed trace elements. Chromium, copper, fluoride, iodine, iron, manganese, molybdenum, selenium, and zinc are some of the replaceable trace elements. These essential micronutrients with a variety of essential functions are involved in many physiological and biochemical processes.[1]

A number of advances have occurred with respect to biomaterials, surgical instrumentations, operating room design, prosthetic materials, surgical techniques, and invasive and non-invasive screening techniques during the last few decades. Despite these improvements, there are still considerable postoperative morbidities in the field of congenital cardiac surgery.[2] Relevantly, alterations in the level of micronutrients with essential functions may increase morbidity in the group of children. Therefore, it is reasonable to know about the status of trace elements in children undergoing cardiopulmonary bypass. Reductions in some of the trace element levels after cardiopulmonary bypass already were reported by some authors;[3–6] however, the number of trace elements that can be measured were limited in these reports. As another topic, it was reported that cyanotic CHD patients have significantly lower levels of serum selenium and zinc levels when compared with the healthy population.[7]

The aim of this study was to evaluate the alterations in serum copper, chromium, manganese, selenium, magnesium, zinc, iron, arsenic, boron, and silicon levels in children with cyanotic and acyanotic CHD who underwent cardiac surgery with cardiopulmonary bypass.

Materials and methods

Features of the patients

This prospective study consisted of 64 patients with CHD and 30 demographically matched healthy control subjects. This study was carried out using the database of a tertiary cardiac centre between June, 2014 and January, 2015. All the patients underwent open-heart surgery for CHDs under cardiopulmonary bypass. A total of three groups were formed. Patients with

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acyanotic CHD comprised the acyanotic group (n = 34). Oxygen saturation on pulse oximetry (SpO_2) and arterial blood sample (SaO_2) <93% is defined as cyanosis in patients without oxygen supplement and coexisting mixing intracardiac pathology. Patients with cyanotic CHD comprised the cyanotic group (n = 30). The control group consisted of 30 healthy children with normal echocardiographic evaluations. Power analysis revealed that the sample sizes for each group were at least 30 (0.80, α: 0.05). Patients with previous open-heart surgery, systemic disease, growth retardation, infectious or genetic disorders, and metabolic diseases were excluded from the study. During this period, 2–250 patients were operated. A total of 70 patients between the percentiles 3th–97th who agreed to participate were included in the study; six patients' blood samples were centrifuged inappropriately. The control group consisted of patients who visited our outpatient clinic and patients with no cardiac pathology. Finally, 94 subjects were divided into the acyanotic patient group (n = 34), cyanotic patient group (n = 30), and control group (n = 30). Patient characteristics are shown in Table 1. The study was approved by the institutional ethics committee (approval number: 2014-01). The study was also conducted in accordance with the Declaration of Helsinki. Informed consents were obtained from the patients' families.

Surgery

Standard general anaesthesia was administered to all patients. Surgery was performed through median sternotomy. Cardiopulmonary bypass was performed using a roller pump and the Capiox Fx 05 oxygenator (Terumo Cardiovascular Systems, Ann Arbor, Michigan, United States of America)/Capiox Fx 15 oxygenator (Terumo Cardiovascular Systems) with an incorporated cardiotomy reservoir. The pump was primed with Ringer's solution, fresh frozen plasma, erythrocyte suspensions depending on the haematocrit value of the patient. In addition, 20% mannitol (2 ml/kg) and 8.4% sodium bicarbonate (1 mmol/kg) were used during priming. Anticoagulation was provided by intravenous administration of heparin (300 U/kg). The activated clotting time values were maintained at >480 seconds during the surgery. Cardiopulmonary bypass was established from the aorta and the caval veins or the right atrium. The nasopharyngeal temperature was maintained between 28 and 34°C during cardiopulmonary bypass. The blood flow rate through the pump was adjusted to be between 2.2 and 2.6 L/m^2. Moderate haemodilution, a haematocrit of 38–34%, was used. Warm blood cardioplegia was utilised every 20 minutes during the cross-clamp period. Next, 20 mg/kg magnesium sulphate (15% 10 ml) was injected into all of the cardiplegia doses. After discontinuation of cardiopulmonary bypass, heparin was neutralised with an equipotent dose of protamine sulphate.

Blood sample collection

The measured biochemical parameters were serum levels of copper, chromium, manganese, selenium, magnesium, zinc, iron, arsenic, boron, and silicon in all groups. Baseline first samples were withdrawn from a cubital vein and transferred into heparinised tubes ~ 30 minutes before surgery. The central venous line was used as the second blood sample, which was taken 1 hour after the sternum was closed. All samples were stored at 4°C. Serum samples were centrifuged at 1500 × *g* for 10 minutes and stored at −80°C until analyses in 1 hour.

Measurement of trace elements

Serum trace elements were determined by Inductively Coupled Plasma Optical Emission Spectrometer-ICAP 6000 by Thermo, Cambridge, United Kingdom. Before analysis, serum samples were filtered, and 1 ml of serum was diluted in 0.3% HNO_3 to 10 cc and vortexed. The standard concentrations were prepared from 1000 ppm stock solution procured from the chemistry laboratory for standard graph calibration. A spectrophotometric method for the analysis of all elements had a linear calibration curve for chromium, manganese, and selenium standards of 50 and 100 ppb; for copper, iron, magnesium, and zinc standards of 500 and 1000 ppb; for arsenic, boron, and silicon of 50, 100, and 1000 ppb. Absorbance of chromium, manganese, selenium, copper, iron, magnesium, zinc, arsenic, boron, and silicon were read at 267.7, 257.6, 196.0, 324.7, 259.9, 285.2, 206.2, 189.0, 249.7, and 251.6 nm, respectively. The correlation coefficient of the lines were ~ 1 (0.999 for most analytes). Multiple wavelengths were generally monitored for each element to provide confirmation of the quantitative results, but only one wavelength is reported for each element. Calibration standards and samples for analysis of whole blood were monitored in the radial mode at all wavelengths, whereas analysis of serum samples at all wavelengths was performed in both modes of observation (axially and radially).

Data collection

Hospital charts, echocardiographic and cardiac catheterisation data, and operative reports of the patients were prospectively recorded. The Aristotle scores,[8,9] the Society of Thoracic Surgeons and European Association for Cardiothoracic Surgery Mortality Categories,[10] and Risk Adjustment for Congenital Heart Surgery Scores[11] of the patients were calculated.

Statistical method

Statistical calculations were performed with Number Cruncher Statistical System 2007 Statistical Software (UT, United States of America) programme for Windows. Besides standard descriptive statistical calculations (mean, standard deviation, and median), the Friedman test was used for multiple groups. The Mann–Whitney U test was used for the comparison of two groups. The Dunn's multiple comparison test was carried out for subgroup analysis. Pearson's correlation tests were performed for establishing associations between parameters. Statistical significance level was established at $p < 0.05$.

Results

There was no significant difference ($p < 0.05$) between both patient groups and control group in terms of preoperative demographics (Table 1). Details on CHDs of each group are given in Table 2.

According to the operative and early postoperative data of patients, it was found that the cyanotic group had significantly longer cardiopulmonary bypass times ($p < 0.0001$), cross-clamp times ($p < 0.0001$), and longer intensive care stay ($p = 0.029$) and hospital stays ($p = 0.034$) compared with the acyanotic group (Table 3).

In the cyanotic group, extracorporeal membrane oxygenation support was needed in one patient, pneumonia was observed in two patients, junctional ectopic tachycardia was observed in two patients, pneumothorax was observed in one patient. In the acyanotic group, pneumonia was observed in one patient, pericardial effusion occurred in one patient, and junctional ectopic

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Table 1. Preoperative demographic data.

	Control group (n = 30)	Acyanotic group (n = 34)	Cyanotic group (n = 30)	p
Age (month)	30 ± 34	34 ± 30	24 ± 30	0.318
Weight (kg)	12.41 ± 8.8	15.95 ± 12.86	10.87 ± 10.79	0.216
BSA (m^2)	0.54 ± 0.28	0.69 ± 0.43	0.67 ± 0.94	0.763
Gender (M/F)	17/13	19/15	13/17	0.815
Arterial blood saturation		98.3 ± 1.1	85.7 ± 6.7	0.003
Aristotle-B score		5.78 ± 2.14	8.34 ± 1.58	0.0001
Aristotle-C score		6.1 ± 2.51	9.31 ± 1.83	0.0001
RACHS score		2.05 ± 0.95	2.7 ± 0.66	0.016
STS-EACTS MC		1.85 ± 1.09	2.85 ± 0.88	0.003

Aristotle-B score = basic Aristotle score; Aristotle-C score = comprehensive Aristotle score; BSA = body surface area; F = female; M = male; RACHS = Risk Adjustment for Congenital Heart Surgery Score; STS-EACTS MC = the Society of Thoracic Surgeons and European Association for Cardiothoracic Surgery mortality categories
Values are expressed as the mean ± SD
$p < 0.05$ was accepted to be statistically significant

Table 2. CHDs in each group.

Acyanotic group	N	Cyanotic group	n
Artrial septal defect	12	Tetralogy of Fallot	10
Ventricular septal defect	12	Pulmonary stenosis with ventricular septal defect	7
Antrioventricular septal defect	4	Single ventricle pathology	7
Aortic valve stenosis	2	Transposition of great arteries	3
Aortic arch hypoplasia with ventricular septal defect	2	Total anomalous pulmonary venous connection	2
Arcus aorta hypoplasia and aortic valve stenosis	1	Truncus arteriosus	1
Aortic valve stenosis and ascending aorta aneurysm			

Table 3. Comparison of operative and early postoperative values between the study groups.

Variables	Acyanotic group (n = 34)	Cyanotic group (n = 30)	p
CPB time (minutes)	93.11 ± 52.34	139.1 ± 38.88	0.0001
AXC time (minutes)	57.92 ± 38.89	93.64 ± 27.57	0.0001
Length of ICU stay after surgery (days)	2.78 ± 2.38	9 ± 16.75	0.029
Length of hospital stay after surgery (days)	9.16 ± 3.56	15.81 ± 18.24	0.034
MV time (hours)	22.73 ± 31.61	48.68 ± 75.09	0.253
Ultrafiltration (ml)	192.86 ± 101.77	185.71 ± 121.5	0.697
Body temperature during CPB (°C)	31.78 ± 2.68	31.5 ± 2.59	0.779

AXC = aortic cross-clamp; CPB = cardiopulmonary bypass; MV = mechanical ventilation
Values are expressed as the mean ± SD
$p < 0.05$ was accepted to be statistically significant

tachycardia was observed in one patient. Regarding the total number of complications, there was no statistical difference between the groups. There was no in-hospital mortality.

The baseline serum levels of arsenic, manganese, and zinc of both patient groups were lower than controls but there was no significant difference between the baseline serum trace element levels of the cyanotic and acyanotic groups. In both patient groups, there was a significant decrease in postoperative serum levels of copper and zinc and a significant increase in iron and magnesium levels. Silicon increased significantly only in the cyanotic group. No significant difference was detected between postoperative serum trace element levels of the cyanotic and acyanotic groups. Postoperative serum arsenic, boron, copper, and zinc levels in both groups remained low compared with the control group, whereas the silicon and iron values were observed to remain high (Table 4).

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Table 4. Comparison of serum trace element levels.

	Acyanotic group (n = 34)	Cyanotic group (n = 30)	p	Control group (n = 30)	p
As					
Preoperative	65.2 ± 17.3	64.9 ± 15.3	0.258	82.3 ± 11.1	0.003
Po 1 hour	67.3 ± 14.3	67.6 ± 12.9	0.944		0.0001
P	0.701	0.926			
B					
Preoperative	0.8 ± 1.1	1.0 ± 1.3	0.539	1.3 ± 2.3	0.390
Po 1 hour	0.5 ± 0.6	0.5 ± 0.8	0.885		0.030
p	0.319	0.114			
Si					
Preoperative	74.3 ± 49.2	62.5 ± 41.1	0.362	65.2 ± 47.5	0.571
Po 1 hour	88.4 ± 45.1	88.8 ± 42.5	0.968		0.003
p	0.093	0.044			
Cr					
Preoperative	0.2 ± 0.6	0.1 ± 0.2	0.036	0.1 ± 0.5	0.077
Po 1 hour	0.2 ± 0.3	0.1 ± 0.4	0.269		0.490
p	0.482	0.553			
Cu					
Preoperative	121.1 ± 36.5	121.7 ± 47.4	0.955	126.8 ± 34.4	0.884
Po 1 hour	100.1 ± 31.7	99.6 ± 26.6	0.951		0.008
p	0.009	0.027			
Fe					
Preoperative	76.7 ± 50.2	88.9 ± 54.0	0.405	111 ± 32.0	0.512
Po 1 hour	269 ± 149.9	287.5 ± 137.5	0.617		0.0001
p	0.0001	0.001			
Mg					
Preoperative	2270.2 ± 412.0	2312.1 ± 406.6	0.715	2287 ± 521.0	0.943
Po 1 hour	2764.7 ± 820.1	2878.1 ± 890.4	0.604		0.055
p	0.001	0.043			
Mn					
Preoperative	0.1 ± 0.1	0.1 ± 0.1	0.551	0.5 ± 0.3	0.0001
Po 1 hour	0.1 ± 0.4	0.1 ± 0.2	0.481		0.0001
p	0.153	0.888			
Se					
Preoperative	7.7 ± 2.5	7.4 ± 1.7	0.541	7.1 ± 2.4	0.618
Po 1 hour	8.0 ± 1.9	7.6 ± 0.9	0.144		0.453
p	0.253	0.478			
Zn					
Preoperative	91.2 ± 18.6	92.1 ± 26.5	0.881	111.5 ± 26.8	0.013
Po 1 hour	78.7 ± 25.4	71.0 ± 20.2	0.198		0.0001
p	0.033	0.028			

Po = postoperative 1 hour; As = arsenic; B = boron; Cr = chromium; Cu = copper; Fe = iron; Mg = magnesium; Mn = manganese; Se = selenium; Si = silicon; Zn = zinc
Values are expressed as the mean ± SD
Trace element levels are in microgram/decilitre (μg/dl)
$p < 0.05$ was accepted to be statistically significant

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Pearson's correlation analysis showed that there was no correlation between operative and postoperative parameters and trace element levels in the acyanotic group. Postoperative serum levels of copper ($r = -0.895$, $p = 0.003$) and zinc ($r = -0.87$, $p = 0.005$) were negatively correlated with the ultrafiltration volume in the cyanotic group. Magnesium levels ($r = -0.402$, $p = 0.037$) were negatively correlated with cooling temperatures in cyanotic group.

Discussion

This study describes the trace element levels of children with cyanotic and acyanotic CHDs who underwent cardiac surgery with cardiopulmonary bypass. Copper, which is one of the important trace element, plays an important role in the structure of many enzymes. A few examples of these enzymes are superoxide dismutase, lysyl oxidase, and cytochrome C oxidase.[12] In a study published by Melnikov et al.[13] including 21 children, the level of copper decreased significantly at the end of cardiopulmonary bypass, but returned to preoperative values 24 hours after surgery. In adult cardiac surgery, Yan et al.[6] showed decreased concentrations of blood copper at the onset of cardiopulmonary bypass that reached lower levels at the end of cardiopulmonary bypass. The authors showed that concentrations of copper was recovered at postoperative day 6. In an in vitro study, McDonald et al.[14] showed a reduction in circulating levels of copper by 18.2%. The authors also declared that there is no advantage in using a prime solution including albumin over other solution types from the trace element level point of view for the time of period after cardiopulmonary bypass.[14] In the present study, baseline copper levels that we measured were similar among the groups. According to the postoperative values, there was a significant depletion in copper levels in both patient groups ($p = 0.002$). As it has been suggested by Zamparelli et al.,[15] alterations in copper levels may be related to the haemodilution during cardiopulmonary bypass. In cyanotic patients, the decrease in copper levels can be explained by the effect of ultrafiltration because of the negative correlation between copper levels and ultrafiltration volume.

Chromium activates the insulin receptor kinase and potentiates the action of insulin.[1,16] In addition to this, it has been reported that chromium levels are low in patients with diabetes mellitus.[17] To the best of our knowledge, chromium levels have not been studied after cardiopulmonary bypass so far. In this study, there was no statistically significant difference in view of the baseline chromium levels between both study groups and control group. In addition, there was no significant alteration in chromium levels of cyanotic and acyanotic groups after on-pump surgery.

Selenium is pivotal in the antioxidant defence system. It is associated with selenoproteins such as glutathione peroxidase, thioredoxin reductase, and iodothyronine 5'-deiodinase.[18] Low levels of blood selenium are associated with increased morbidity in both cardiac[19] and non-cardiac critically ill patients.[20,21] A level of selenium under 0.7 mmol/L was shown to be associated with threefold increase in morbidity in critically ill patients.[20] Stoppe et al.[3] showed an association between low level of selenium and increased incidence of postoperative multiple organ failure in a study including 60 patients who underwent on-pump cardiac surgery. Al-Bader et al.,[22] in adult patients, showed a significant and rapid depletion in serum selenium levels after cardiopulmonary bypass. In an in vitro study, the authors demonstrated a reduction of 17.1% in circulating selenium levels compared with baseline levels.[14] The present study showed that there is no difference in baseline selenium levels between the cyanotic group, the acyanotic group, and the control group. There was no significant alteration in selenium levels in the cyanotic and acyanotic groups after on-pump surgery.

Manganese plays an important role in redox reactions. It catalyses superoxide dismutase, ribonucleotide reductase, and oxygen complexes.[23] Manganese deficiency may cause hypercholesterolaemia and weight and protein loss.[1] To the best of our knowledge, there are no previous reports with regard to alterations in manganese levels due to cardiopulmonary bypass effects. In both the patient groups, there was no statistically significant alteration in manganese levels after on-pump surgery. On the other hand, manganese levels were significantly lower in both cyanotic and acyanotic groups compared with control patients. More studies are required to explain the clinical significance of these results.

Zinc has a crucial role in protein synthesis and metabolism of nucleic acids, carbohydrates, and lipids.[5] Zinc has cardioprotective properties such as decreasing catecholamine-induced injury and decreasing re-perfusion arrhythmia.[24] Ghaeman et al.[25] detected profound hypozincaemia in advanced stage congestive heart failure patients. In a previous study, a significant decrease in serum zinc levels were shown after the onset of cardiopulmonary bypass. In the same study, zinc levels started to recover after cease of cardiopulmonary bypass but remained low. It returned to initial values on postoperative day 6 in both coronary artery bypass grafting and valve replacement patients.[6] In an in vitro study, authors demonstrated a reduction of 29% in circulating selenium levels compared with precircuit baseline values.[14] In the present study, initial serum values were similar in both cyanotic and acyanotic groups but lower compared with the control group values. Post-bypass serum zinc values decreased significantly in both patient groups. Similar to some previous reports, redistribution and haemodilution may be the reason for the lower zinc level in these patients.[5] In cyanotic patients, the decrease in zinc levels can be explained by the effect of ultrafiltration because of the negative correlation between zinc levels and ultrafiltration volume.

Magnesium is an important component of cell membranes and enzymes. Magnesium effects resting membrane potential of cardiac cells and also reduces the risk of re-entry by increasing relative refractory period.[26–28] An animal study demonstrated the cardioprotective role of magnesium pre-treatment in ischaemia re-perfusion injury.[29] Marinque et al.[30] showed that the incidence of postoperative junctional ectopic tachycardia can be reduced by magnesium sulphate administration during the re-warming phase of cardiopulmonary bypass. In adult cardiac surgery, the role of magnesium in postoperative atrial fibrillation in unclear or controversial. Some authors suggested that hypomagnesaemia is associated with increased incidence of atrial fibrillation after cardiac surgery.[31,32] The present study demonstrated that there is no difference in baseline magnesium levels between cyanotic patients, acyanotic patients, and controls. Magnesium levels increased significantly when compared with baseline levels, but are not significantly higher compared with control values. This increase was due to magnesium administration in cardioplegia during cardiopulmonary bypass.

To the best of our knowledge, there are reports in the literature examining the relationship between changes in blood levels of arsenic, boron, and silicon and cardiopulmonary bypass.

The present study showed a statistically significant increase in silicon levels in cyanotic patients compared with acyanotic and control patients. This difference was not related to cardiopulmonary bypass time. Alteration in silicon levels may be related to the components of the circuit that was made of silicon. Venous, and cardiotomy, filters are coated with silicone, simethicone, and methylcellulose containing antifoam products.[33] In addition, pumpheads contain silicon.[34]

In our study, postoperative serum iron levels increased in both patient groups, but there was no difference between groups. This may be due to the contact of blood with the foreign surface, haemolysis caused by blood cardioplegia solution, or ischaemic re-perfusion injury; however, there was no significant correlation found for this result. In our view, this increase may be due to the haemolysis that occurs because of the contact of erythrocytes with the foreign surface.

Regarding postoperative complications, there was no correlation between levels of postoperative trace elements and complications. We could not evaluate any correlation between mortality and trace element levels because no mortality was observed in patient groups. In the present study, the Aristotle scores, the Society of Thoracic Surgeons and European Association for Cardiothoracic Surgery Mortality Categories, and Risk Adjustment for Congenital Heart Surgery scores were higher in cyanotic patients compared with acyanotic patients. Prolonged cross-clamp, cardiopulmonary time, and ICU stay may be the result of high scores.

Chuchwell et al.[35] showed removal of chromium, copper, manganese, selenium, and zinc in their in vitro haemodialysis model. In the same study, they found small amounts of chromium, copper, selenium, and zinc in the dialysate of the in vivo model.[35] In the present study, we found a negative correlation between ultrafiltration volume and copper and zinc in cyanotic patients. This may be one of the causes of serum zinc and copper decrease after cardiopulmonary bypass; however, this correlation was not detected in acyanotic patients.

Taggart et al.[36] reported that systemic cooling to 20°C modifies iron and zinc concentrations and the protein-binding ratios of these trace elements during on-pump surgery; however, this effect did not continue in the postoperative period. In our study, there were no correlation between iron and zinc levels and systemic cooling temperature in both groups. The present study, however, showed a negative correlation between magnesium levels and systemic cooling temperature in cyanotic patients. Although we could not detect any correlation between cross-clamp and cardiopulmonary bypass times, this correlation might be related to higher cardiopledgia use in operations with deeper body temperatures due to longer cooling–warming phases.

As mentioned above, previous studies have shown that some of the trace elements reach normal values within a few days after on-pump surgery.[6] On the basis of previous studies, low levels of trace elements may not require early replacement. Future studies will allow us to make a definitive prediction on this subject.

In conclusion, copper, chromium, selenium, magnesium, iron, boron, and silicon levels in patients with CHD are similar to healthy control patients; however, arsenic, manganese, and zinc levels are lower in the patients with CHD in comparison with healthy children. After cardiopulmonary bypass, copper and zinc levels in cyanotic and acyanotic patients decrease, whereas magnesium and iron levels increase. Silicon level increases in cyanotic patients.

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Conflicts of Interest. None.

Ethical Standards. The study was approved by the institutional ethics committee (approval number: 2014-01). The study was also conducted in accordance with the Declaration of Helsinki. Informed consents were obtained from the patients' families.

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