

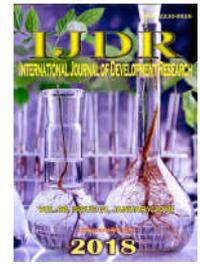


ISSN: 2230-9926

Available online at <http://www.journalijdr.com>

# IJDR

International Journal of Development Research  
Vol. 08, Issue, 01, pp.18321-18325, January, 2018



ORIGINAL RESEARCH ARTICLE

OPEN ACCESS

## THE IMPORTANCE OF THE STUDY OF PLASMA CONCENTRATION OF SELENIUM AND OXIDATIVE STRESS IN CARDIAC SURGERY WITH CHILDREN CARDIOPULMONARY BYPASS

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### ARTICLE INFO

#### Article History:

Received 28<sup>th</sup> October, 2017  
Received in revised form  
17<sup>th</sup> November, 2017  
Accepted 10<sup>th</sup> December, 2017  
Published online 31<sup>st</sup> January, 2018

#### Key Words:

Plasma concentration of Selenium,  
Oxidative stress, Cardiac surgery with  
children cardiopulmonary bypass.

### ABSTRACT

**Background:** Several studies have evaluated the importance of the recovery of adults and children in cardiac surgery with cardiopulmonary bypass. Moreover, little is known about the plasma concentration of Selenium of the Brazilian children's population in the pre-, intra- and post-operative with cardiopulmonary bypass.

**Objective:** To evaluate the current Brazilian literature on cardiac surgeries in children with cardiopulmonary bypass that addresses the damage caused by oxidative stress and its relation with plasma concentration of selenium.

**Methods:** An electronic systematic database search (MEDLINE, PUBMED, PsycINFO, and EBM Reviews) was performed to identify articles concerning the plasma concentration of Selenium and oxidative stress in cardiac surgery in children with cardiopulmonary bypass.

**Results:** There are no scientific evidences and clinical data on the plasma concentration of Selenium and its relation with oxidative stress in cardiac surgery with children cardiopulmonary bypass in Brazil.

**Conclusion:** Selenium supplementation and therapy after cardiac surgery, focusing on the pathophysiology of oxidative stress and the clinical usage of selenium should be performed in Brazil. There is an importance and the necessity of the study of plasma concentration of Selenium and oxidative stress in cardiac surgery with children cardiopulmonary bypass.

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**Citation:** Marlice Oliveira de Oliveira Ulbrecht, Lourdes Z. Zanoni, Daniel Araujo Gonçalves, Vitor Paulo Campos, Elaine Silva de Pádua Melo, Rita de Cassia Avelhaneda Guimarães and Valter Aragão do Nascimento, 2018. "The importance of the study of plasma concentration of Selenium and oxidative stress in cardiac surgery with children cardiopulmonary bypass", *International Journal of Development Research*, 8, (01), 18321-18325.

## INTRODUCTION

Congenital heart defects are defined as abnormalities in cardiovascular structure or function that are present at birth. Although Brazil has achieved the goal of reducing infant mortality established for 2015, rates are still high, especially with regard to the neonatal component. Early neonatal mortality represents about 60% to 70% of infant mortality, and 25% of deaths occur on the first day of life. Congenital heart defects correspond to about 10% of infant deaths and 20% to

40% of deaths due to malformations (Ministry of Health - National Plan for Assistance to the Child with Congenital Heart Disease, Ordinance N ° 1,727; OF JULY 11, 2017). Cardiopulmonary bypass (CPB) is a form of extracorporeal circulation (ECC). In extracorporeal circulation the pumping functions of the heart are replaced by a mechanical pump. As well as functions of the lungs are replaced by an apparatus that makes the exchanges of gases with the blood. However, despite the technological advances, pulmonary dysfunction in the postoperative period of cardiac surgery with extracorporeal circulation remains one of the most important causes of morbidity and mortality. Ischemic reperfusion injury may lead to myocardial dysfunction with low cardiac output syndrome (Brix-Christensen Conti, 2001). Selenium is a trace element

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essential component of several major metabolic pathways, including thyroid hormone metabolism, antioxidant defense systems as well as immune function (Brown and Arthur, 2001). It also acts as an antimutagenic agent, preventing malignant transformation of normal cells. Such protective effect of selenium was associated with its presence glutathione peroxidase which is an enzyme known for its antioxidant action, protecting the DNA and other cellular components from oxidative damage (Almond *et al.*, 2010). In fact, the antioxidant action of glutathione protects the lipids of membranes and other cellular constituents against oxidative damage through the unfolding of hydrogen peroxide and hydroperoxides of fatty acids (Broome *et al.*, 2004; Hoffman *et al.*, 2010). Serum selenium concentrations in a given population exhibit regional differences as well as between countries. In fact, concentrations are strongly influenced by geological and geochemical factors (Alfhan, Neve, 1996). However, Muntau *et al.* (2002) in their studies involving different countries, has verified that in children the serum concentration of selenium is less pronounced than those reported for adults. That is, mean serum selenium concentrations in adults range from 49.7 to 197  $\mu\text{g}$ , while overall mean values in children range from 48.1 to 126.3  $\mu\text{g}$ . The increase of oxidative stress markers after cardiac surgery with extracorporeal circulation may play an important role in ischemic reperfusion injury. Several factors may be involved including myocyte lesions by reactive oxygen species (Brix-Christensen, 2001; Carmona, Manso, Vicente, 2008). Reactive oxygen species play an important role in reperfusion injury of ischemia and in myocardial stunning in adults. On the other hand, the reactive species of oxygen suffer an increase in children after extracorporeal circulation, which are more susceptible to oxidative stress (Laffey, Boylan, Cheng, 2002; Calza, Lerzo, Perfumo, 2002; Christen, Finckh, Lykkesfeldt, 2005). In view of the above, it is necessary to carry out a bibliographic study that reports if there are in Brazil studies on the plasma changes of selenium and its relation with oxidative stress in the pediatric cardiac surgery with extracorporeal circulation. Analysis of these changes as stress markers may contribute to reduce postoperative complications. According to the Ministry of Health - National Plan for Assistance to Children with Congenital Heart Disease (Ordinance No. 1,727, OF JULY 11, 2017), a nutritional assistance for assessing heart disease is necessary based on the evaluation and adequacy of nutritional recommendations for each stage of childhood associated with congenital heart disease.

### General considerations

Congenital heart defects are mostly treated surgically and the success of the procedure is the result of early diagnosis, as well as technological advances and surgical techniques. Technological advances such as the development of extracorporeal circulation (CPB) have created new possibilities for curing congenital heart disease. New technologies involving cardiac surgeries have allowed the emergence of new knowledge regarding the physiology of the blood circulation, as well as the reactions of the organism to the surgical aggressions. In fact, a better understanding of the maintenance of electrolyte balance, basic acid and cellular metabolism has also been improved. However, despite technological advances, postoperative pulmonary dysfunction of cardiac surgery with extracorporeal circulation continues to be one of the most important causes of morbidity and mortality (Conti, 2001).

CPB causes a systemic inflammatory response syndrome, which is triggered due to several factors such as blood contact with the non-physiological surfaces of the materials that make up the equipment, surgical trauma or phenomena resulting from myocardial ischemia, myocardial reperfusion and changes in temperature body. The systemic inflammatory response in which it is potentially responsible for the activation of neutrophils (Morse, Adams, 1998), together with the high oxygen tension used during CPB, are important sources of free radicals responsible for oxidative stress (Ihnken, Morita, Buckberg, 1998; Bruckeck *et al.*, 2006). Such situations mentioned in the previous paragraph produce signs and symptoms known as Post - Perfusion Syndrome, which may compromise the heart, lungs, kidneys and other organs. The body reacts by activating defense mechanisms to protect the affected tissue from the aggressor (Moura; Pomerantzeff; Gomes, 2001; Calvin *et al.*, 2002).

In addition to the non-physiological hemodynamic conditions during CPB, the changes resulting from the myocardial ischemia-reperfusion phenomenon are quite significant. In addition to the non-physiological hemodynamic conditions during CPB, the changes resulting from the myocardial ischemia-reperfusion phenomenon are quite significant. On the other hand, in the period of reperfusion when circulation is restored, the production of large amounts of free radicals and activation of neutrophils occurs. These free radicals are responsible for considerable cellular damage, both structural and functional, involving damage to the lipid membrane, protein denaturation, inactivation of enzymes and DNA alterations. Reperfusion injury is closely related to cardiac function impairment and postoperative complications (Christen *et al.*, 2005; Kunt *et al.*, 2006). Results published by Bolli *et al.* (1989) demonstrated that 50% to 70% of myocardial dysfunction after cardiopulmonary bypass are due to the appearance of free radicals, which are released during the first minutes of reperfusion. The lungs are responsible for neutralizing most biochemical mediators, but during CPB they are perfused only by the bronchial arteries, causing ischemic damage due to excessive accumulation of metabolic substances in the pulmonary interstitial fluid. After the removal of the aorta and the return of the heartbeat, the reperfusion injury begins through the existence of oxygen free radicals in the blood that will affect the lungs (Edmo Atikue, 2007). Renal insufficiency, severe blood dyscrasias, metabolic acidosis, prolonged shock, and depression of left ventricular function due to CPB surgery have been associated with inflammatory response and systemic oxidative stress (Brix-Christensen, 2001). Although several damages occur due to CPB, selenium plays an anti oxidant role and also participates in the metabolism of thyroid hormones through the enzyme thioredoxin reductase (Alissa; Bahijri; Ferns, 2003; Ross *et al.*, 2012).

In a study involving healthy adults in Latin America performed by Fonseca (2010), the plasma concentration of selenium obtained was  $91.51 \pm 18.78 \mu\text{g/L}$ . However, in a study conducted in the city of Rio de Janeiro (Brazil) by Da Cunha *et al.* (2013), the selenium concentration ranged from 56.5 to 94.5  $\mu\text{g/L}$  with a mean of 73, 2  $\mu\text{g/L}$ . In Campo Grande, central western Brazil, studies involving the dynamics of copper, zinc and oxidative stress during cardiac surgery with CPB in adults were performed by Dias *et al.*, (2012). According to Nunes *et al.*, (2010), the mean values for the study population in the Brazilian States as São Paulo and

Minas Gerais were 113  $\mu\text{g/L}$ , in Goiás it was 95  $\mu\text{g/L}$ , Rio Grande do Sul reached an average of 111.5  $\mu\text{g/L}$  and in the State of Pará of 188.5  $\mu\text{g/L}$ , Pará being the State from which the "Pará nut" is the main source of those mineral. According to Da Silva *et al.*, (2013), in individuals living in the Tapajós / Amazonas River region, a mean mineral concentration of 135  $\mu\text{g/L}$  was identified, which is one of the highest concentrations in the Brazilian territory due to habits the local population, which includes Brazilian nuts and fish.

The pediatric population is at greater risk for selenium deficiency. Due to nutritional changes after birth, selenium concentrations are expected to be much more heterogeneous in this group than in an adult population. Pediatric patients undergoing surgical treatment for the correction of cardiac malformations present greater postoperative complications than adults. Stoppe *et al.*, (2011) demonstrated that cardiac surgery with CPB resulted in an important intraoperative reduction of levels of antioxidant trace elements, such as selenium, copper and zinc. It also showed that the low rates of selenium dosage in the immediate postoperative period was a predictor factor for the development of multiple organ failure and increased hospital stay rate. Some factors may contribute to variations in selenium concentrations. Short-term physiological influences such as quality and food intake, as well as long-term influences such as age, sex and race (Alfthan; Neve, 1996). Plasma differences can be justified mainly due to the dietary habits. It is known that the concentration of selenium in soils varies widely between countries, even between regions of the same country. It is the case of soils of the northern region of Brazil, rich in selenium, a fact that is responsible for the high concentrations of this element in the chestnut of Pará (*Bertholletia excelsa*) produced in that region. Studies on pediatric cardiac surgery and dynamics of copper and zinc are known (Zanoni, Melnikov, 2008). However, studies involving the evaluation of oxidative stress as well as the plasma concentration of selenium in CPB surgeries have not yet been performed for children.

## MATERIALS AND METHODS

The electronic databases Medline (National Library of Medicine, USA), SciELO (Scientific Electronic Library Online) and PubMed in the last ten years were used as search criteria for published articles. The review looked for studies involving the importance of the study of plasma concentration of Selenium and its relation with oxidative stress. The words used as descriptors were selenium and cardiopathies in children, macro elements and microelements and oxidative stress. Regarding the search for articles published in Brazil, the words used were "Brazil", thematic area "health sciences and cardiology, oxidative stress" and "infant cardiology", extracorporeal surgery in children. As a complementary part of this manuscript, we also carried out a consultation on the databases of the Unified Health System (SUS – Sistema Único de Saúde).

The identification and selection of articles were carried out by the research group component independently. The search period in the electronic bases was from the year 2007. In this sense, a bibliographical review of epidemiological studies was carried out with the Brazilian population that published their studies involving Selenium and oxidative stress related to childhood cardiomyopathies.

## RESULTS

In Brazilian children's population, there are not scientific papers, theses or dissertations involving studies or clinical evidence on the concentration of selenium and its relations with oxidative stress in the pre-, intra- and post-operative with cardiopulmonary bypass. On the other hand, Brazil has made investments in the area of child health, especially in the area of child cardiology. In several Brazilian states, pediatric cardiovascular surgery is performed in the hospitals enabled by Unified Health System (SUS) in the High Cardiovascular Complexity. There are 69 hospitals in the Brazil where they provide assistance to patients with cardiovascular diseases up to the age of 18. Figure 1 show the number of hospitals enabled to perform cardiologic surgeries in each Brazilian state. The name of each of the Brazilian states below is: AL (Alagoas), AM (Amazonas), BA (Bahia), CE (Ceara), DF (Distrito Federal), ES (Espírito Santo), GO (Goiás, MA (Maranhão), MG (Minas Gerais), MS (Mato Grosso do Sul), MT (Mato Grosso), PA (Para), PI (Piauí), PE (Pernambuco), PR (Paraná), RJ (Rio de Janeiro), RN (Rio Grande do Norte), RS (Rio Grande do Sul), SC (Santa Catarina), SE (Sergipe) e SP (São Paulo). As we can see in Figure 1, there are 21 states that have hospitals with Pediatric Cardiovascular Surgery services. However, there are no hospitals qualified for this surgical care in the States of Paraíba, Tocantins, Rondônia, Roraima, Amapá and Acre.

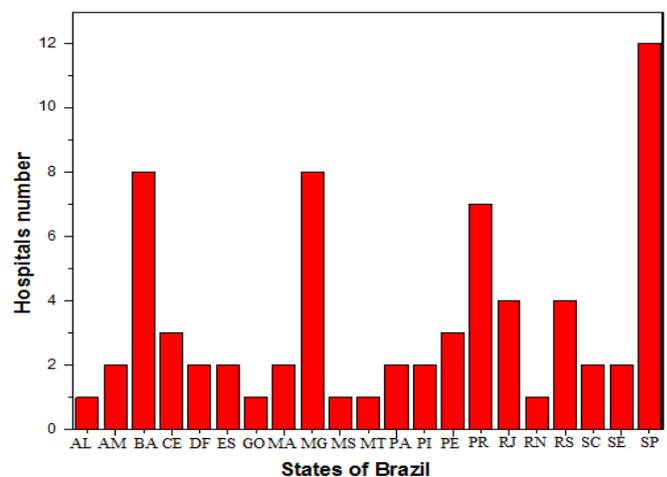
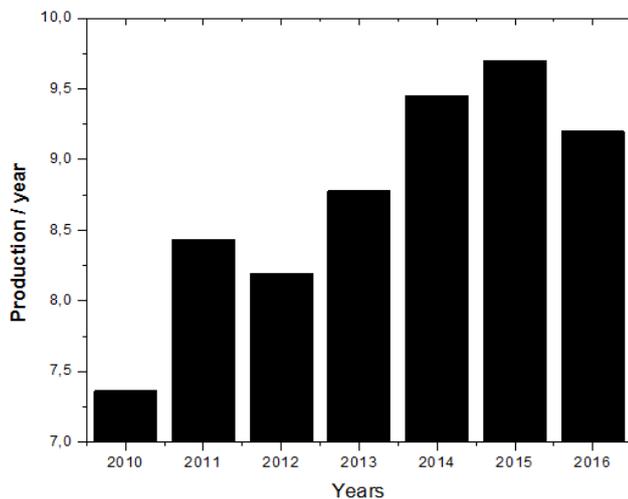


Figure 1. Number of hospitals enabled to perform cardiologic surgeries in each Brazilian state

Brazil in recent years has made investments in basic health care services, based on the principle of care and promotion of the health of women, children and adolescents. In 2017, the National Plan for Assistance to the Child with Congenital Heart Disease was approved with the objective of establishing guidelines and integrating actions that favor access to diagnosis, treatment and rehabilitation of the child and adolescent with congenital heart disease, as well as the reduction of morbidity and mortality (Ministry of Health - National Plan for Assistance to the Child with Congenital Heart Disease, Ordinance N ° 1,727; OF JULY 11, 2017). In fact, there was a gradual increase in the period from 2010 to 2016 of the frequency of pediatric cardiovascular surgeries performed in National Health System (Sistema Único de Saúde – SUS) (Figure 2).



**Figure 2. Evolution of the number of pediatric cardiovascular surgeries in SUS year by year from 2010 to 2016. Source: SIH / DATASUS, Mar. 2017**

Manso *et al.*, (2013) in your retrospective secondary analysis of a cohort study, stated that oxidative stress markers thiobarbituric acid reactive substances (TBARS) and carbonyl moieties were not associated with the development of low cardiac output syndrome (LCOS), the mortality-adjusted hospital length of stay (aLOS), or mortality in children after heart surgery with cardiopulmonary bypass (CPB). However, Manso *et al* (2013) does not mention anything about oxidative stress and its relation to plasma concentration of selenium. As well as Carmona *et al* (2008) in his manuscript does not highlight the relation or importance of selenium in surgery with cardiopulmonary bypass. In this study to date, there are no evidences and clinical data on the plasma concentration of Selenium and its relation with oxidative stress in cardiac surgery with children cardiopulmonary bypass.

## Conclusion

There are not scientific studies or clinical evidence about the plasma concentration of Selenium of the Brazilian children's population in the pre-, intra- and post-operative with cardiopulmonary bypass. The evaluation of oxidative stress and plasma concentrations of selenium in children submitted to cardiac surgery with extracorporeal circulation may serve as a basis for possible pre and postoperative corrections aiming at a more favorable clinical course. Clinical studies failed to demonstrate an association between selenium deficiency and cardiovascular outcomes. New experimental and clinical evidence of preoperative selenium supplementation and therapy after cardiac surgery, focusing on the pathophysiology of oxidative stress and the clinical usage of selenium should be performed in Brazil and others countries. In fact, there is a scientific importance and the clinic necessity of the study of plasma concentration of Selenium and its relation with oxidative stress in cardiac surgery with children cardiopulmonary bypass.

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