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THE IMPORTANCE OF THE ANALYSIS OF VITAMINS A, D AND K IN THE PEDIATRIC POPULATION IN THE INTENSIVE CARE UNIT: COMMENTARY ON CLINICAL RESEARCH AND LITERATURE REVIEW

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ABSTRACT

Background: Vitamin A, D and K deficiency is associated with various diseases in the pediactric population and generates negative impact with regard to the outcome of Intensive Care Unit (ICU) stay. This manuscript aimed to report new information on the impact of vitamin A, D and K deficiency in ICU pediatric patients. Methods: The following keywords were used: vitamin A, D and K deficiency, infant's mortality, pediatric intensive care unit. A research was conducted in Pub Med, Medline, Scopus, Web of Science, and Lilacs electronic databases for the studies published up to 1 January 2018. A research was also carried out in the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) up to 1 January 2018. Only articles that best expressed the ratio of vitamin A, D and K deficiency in critically ill patients in ICUs was selected in this study. Results: it was observed a high prevalence of vitamin A, D and K deficiency in pediatric patients in ICUs evaluated in selected studies. Conclusion: For the health professional, it is essential to obtain reliable information on the effect of vitamin A supplementation during the period of hospitalization of the pediatric population in the intensive care unit. Additional studies are needed to assess the potential benefit of optimizing vitamin D status in the pediatric intensive care unit (PICU). There are still doubts about the potential beneficial or detrimental effects of maximal concentrations of vitamin K in the blood. Further studies on vitamin K metabolism are needed to understand the possible link between the development of intraventricular hemorrhag and genetic variants.

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INTRODUCTION

According to WHO results, around 45% of deaths among children under 5 years of age are linked to under nutrition. In fact, malnutrition includes under nutrition (wasting, stunting, underweight), inadequate vitamins or minerals, overweight, obesity, and resulting diet-related non communicable diseases. 52 million children under 5 years of age are wasted. On the other hand, 17 million are severely wasted, 155 million are stunted and 41 million are overweight or obese.

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According to WHO results (Updated May 2017), around 45% of deaths among children under 5 years of age are linked to under nutrition. An interesting question to be highlighted is that in low- and middle-income countries in which rates of childhood overweight and obesity have increased in recent years (WHO, 2017). Despite the economic and medical impacts of the malnutrition for individuals and their families, malnutrition is still a neglected area and too little has been done to address its causes and serious social and economic implications. Nutrition in the pediatric surgical patient in a care unit is complex subject matter. Under nutrition or excess body weight is a frequent in pediatric health care (Daskalou *et al.*, 2016).

According to Bechard *et al.,* (2013), children who are obese are at increased risk for infection, prolonged lengths of stay and probability of death. In the last years, Vitamins A, D and K has been the focus of several scientific researches due to their role in health, and in prevention or treatment of disease.
In view of the above, this manuscript presents a brief commentary on clinical research and literature review articles that address studies involving vitamins A, D and K in pediatric patients in a treatment unit. It is extremely important for physicians, nurses and other health professionals to be up to date with new alternatives for patient care. This manuscript aimed to report new information on the impact of vitamin A, D and K deficiency in ICU pediatric patient Although there are impositions of several health organs suggesting the supplementation of vitamins A, D and K, there is little evidence of supplementation and efficacy in patients of Intensive Care units.

METHODS

A research was conducted in PubMed, Medline, Scopus, Web of Science, and Lilacs electronic databases for the studies published up to 1 January 2018. A research was also carried out in the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) up to 1 January 2018. This study is a bibliographical research, in which explaining a problem from the theories published in articles, WHO manual etc. The following keywords were used: The PubMed and Lilacs were searched using the following keywords: vitamin A, D and K deficiency, infant's mortality, pediatric intensive care unit.

RESULTS AND DISCUSSION

Vitamin A deficiency impairs innate immunity, however, it is required for adaptive immunity and plays a role in the development of T both-helper (Th) cells and B-cells (Stephensen *et al*., 2001). In a study conducted by Quinlan and Hayani (1996), showed that Serum vitamin A and RBP (retinol binding protein) levels were low in children hospitalized with RSV (respiratory syncytial virus) infection and were lower in children admitted to the intensive care unit. However, No benefit of oral vitamin A supplementation was seen for hospitalized children with RSV infection (Quinlan KP1, Hayani KC). Other research claims that vitamin A should not be given to all children to prevent acute LRTIs (lower respiratory tract infections (Chen *et al.*, 2008). Gogia and Sachdev (2011) in their study entitled "Vitamin A supplementation for the prevention of morbidity and mortality in infants six months of age or less" concludes that there are no results proving that maternal postpartum or vitamin A supplementation will lead to a reduction in infant mortality or morbidity in low- and middle-income countries. According to a randomised and quasi-randomised controlled trials, there is no evidence to support the beneficial potential of vitamin A supplementation among neonates at birth in reducing mortality during the first six months or 12 months of life (Haider *et al.*, 2017). On the other hand, according to Imdad *et al.,* (2017), Vitamin A supplementation is associated with a clinically meaningful reduction in morbidity and mortality in children. Although there is controversy regarding the efficacy of vitamin A supplementation in patients with infections, the World Health Organization has continues to recommend vitamin A supplementation for children aged 6 to 59 months (WHO, 2011).

According to WHO (2011) vitamin A supplementation protocols for vulnerable groups, vitamin A in postpartum is effective for mothers and children, but without evidence of morbimortality decrease. According Neves *et al.,* (2015), there are seven studies carried out in Brazil regarding supplementation were found with large vitamin A doses and their possible consequences for the mother-child binomial. No studies were found in Brazil involving vitamin A supplementation in patients admitted to intensive care units. Vitamin D has several roles in the body, helping to maintain the health of bones and teeth, as well as support the health of the immune system, brain, and nervous system. Severe vitamin D deficiency can result in seizures, osteomalacia, or rickets. However, evidence in children and adolescents are sparse concerning what dose corrects vitamin D deficiency rickets (Misra *et al*., 2008; Munns *et al*., 2006). Patients with chronic diseases such as chronic kidney disease (CKD), asthma, cystic fibrosis (CF) and sickle cell disease and malnutrition have the highest risk of vitamin D deficiency (Holick, 2007; Zhou *et al.*, 2006).

According to Sankar *et al*., (2016), there is a high prevalence of vitamin D deficiency in critically ill children. Vitamin D deficient children had a longer duration of ICU stay as compared to others (Sankar *et al.*, 2016). In countries as South India, patients admitted to intensive care units have a large vitamin D deficiency (Ebenezer *et al*., 2016). In contrast to the results obtained by Ebenezer *et al.,* 2016, in the results obtained by Ponnarmeni *et al*., (2016) when studying the prevalence of vitamin D deficiency in critically ill children with sepsis there was not associated with greater severity of illness or other clinical outcomes (Ponnarmeni *et al*., 2016). In Chile, vitamin D deficiency at Pediatric Intensive Care Unit (PICU) admission was prevalent in critically ill children and was associated with adverse clinical outcomes (Bustos *et al*., 2016). According to a prospective observational study carried out in Spain, the incidence of hypovitaminosis D is high in pediatric PICU patients. However, hypovitaminosis D was not associated with a higher prediction of risk-related mortality (Rey *et al*., 2014). In fact, in some countries the vitamin D deficiency is common in the pediatric critical care population. However, a prospective clinical observational study with groups in the pediatric intensive care unit (PICU) performed in Atlanta, points out that in the case of critically ill children with asthma, more scientific research is needed (Hebbar *et al*., 2014). In Brazil, vitamin D deficiency in non-hostile children is common.

A cross-sectional study based on the Brazilian infant population from urban schools, showed that prevalence of vitamin D insufficiency/deficiency was high among the children. In that study, the insulin resistance was the main cardiometabolic alteration associated with this condition (Milagres *et al*., 2017). For the treatment of vitamin D deficiency rickets, there are recommendations from the American Academy of Pediatrics (AAP) for newborn infants, infants, and patients over 12 months of age (Misra *et al*., 2008). In 2008, the AAP increased its recommended daily intake of vitamin D in infants, children, and adolescents to 400 IU (Misra *et al*., 2008). According to McNally *et al*., (2017), Clinical trials are required to determine if optimization of vitamin D status improves critically ill children. There are several research groups have evaluated vitamin D status in critically ill children. However, these studies do not make clear the relationship between vitamin D status, illness

severity, and clinical course. On the other hand, supplementation of oral of vitamin D3 (cholecalciferol) with antibiotics could reduce the duration of illness in children with pneumonia, and reduce the risk of repeat episodes (Manaseki-Holland *et al*., 2010). There is relatively little evidence of comprehensive efforts in studies evaluating vitamin D supplementation in patients admitted to a pediatric intensive care unit. Among the vitamins mentioned above, another essential vitamin to the proper functioning of the body is vitamin K. *Vitamin K* **is** crucial for blood clotting and bone metabolism. Regarding the clinical practices regarding the management of anticoagulation, some recommendations can be found in the literature (Holbrook *et al*., 2012). A pilot study investigated the effects of a dietary supplement with vitamin K2 and vitamin D on the children with Thalassemic osteopathy (TOSP). It was demonstrated especially in the prepubertal group, a significant improvement in the bone mineral density and Z-score at the lumbar spine area of the patients at the sixth and 12th month of the treatment (Ozdemir *et al*., 2013).

Since 1961, the efficacy of neonatal vitamin K prophylaxis (oral or parenteral) in the prevention of early vitamin K deficiency bleeding is firmly established (American Academy of Pediatrics, 1961). In the literature, there are several manuscript on intracranial bleeding due to vitamin K deficiency (Yilmaz *et al*., 2009; Demirören *et al.,* 2004; Matsuzaka *et al*. 1989; Gopakuma *et al*., 2010). In the Netherlands, it is proposed to use of pediatric intensive care registries to assess the efficacy of national vitamin K prophylactic regimens. The Pediatric Intensive Care Evaluation registry allows ongoing monitoring of the incidence of late intracranial vitamin K deficiency bleeding (Visser *et al*., 2011). Bleeding is a common occurrence in intensive-care-unit (ICU) patients. All newborns require phylloquinone after birth to prevent vitamin K deficiency bleeding (Clarke *et al*., 2015). However, little is known about the impact of genetic variants in the vitamin K-dependent coagulation system on the development of intraventricular hemorrhage (IVH) in premature infants (Schreiner *et al*., 2014). According to Parker, (2013), bleeding in patients in pediatric intensive care units is associated with an increased risk of mortality. For Parker, (2013), interventions directed toward correcting the abnormal coagulation test results are generally either not warranted (in the case of liver disease) or not fully successful (in the case of disseminated intravascular coagulation). According to McNinch *et al*., (1985), in life-threatening bleeds, fresh frozen plasma should be administered prior to VK. In preterm infants born of a mother with Crohn disease, careful observation for coagulation is warranted even after vitamin K administration (Fujioka *et al.,* 2017).

A few years ago there were several studies involving vitamin K administration in newborns and incidence of childhood cancer (Draper and Stiller, 1992; Golding *et al*., 1990; Golding *et al*., 1992). On the other hand, others studies concluded that there was no association between the intramuscular administration of vitamin K and childhood leukemia or other cancers (Devesa *et al*., 1987; Ross and Davies, 2000). According to our survey, although we highlight only a few published studies, there are still doubts about the potential beneficial or detrimental effects of maximal concentrations of vitamin K in the blood (Mihatsch *et al*., 2016). Although vitamin K has been administered intramuscularly for years, some countries refuse to do so (Khambalia *et al*., 2012; Burke *et al*., 2015).

Conclusion

For the health professional, it is essential to obtain reliable information on the effect of vitamin A supplementation during the period of hospitalization of the pediatric population in the intensive care unit. Additional studies are needed to assess the potential benefit of optimizing vitamin D status in the pediatric intensive care unit (PICU). Studies affirm that the length of ICU stay leaves children more likely to have vitamin D deficiency There are still doubts about the potential beneficial or detrimental effects of maximal concentrations of vitamin K in the blood. Our findings suggest that additional clinical research is needed to determine whether vitamin supplementation at ICU admission reduces the risk of deficiency and its associated complications throughout ICU admission. Further studies on vitamin K metabolism are needed to understand the possible link between the development of intraventricular hemorrhag and genetic variants.

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