The Effects of Total Parenteral Nutrition on Plasma Aluminium Level in Premature

SEMRA bahar (✉ semraabahar@gmail.com)

TC Saglik Bakanligi Istanbul Sisli Hamidiye Etfal Egitim ve Arastirma Hastanesi

<https://orcid.org/0000-0002-7113-9646>

umut zubarioglu

TC Saglik Bakanligi Istanbul Sisli Hamidiye Etfal Egitim ve Arastirma Hastanesi

Ali Bulbul

TC Saglik Bakanligi Istanbul Sisli Hamidiye Etfal Egitim ve Arastirma Hastanesi

Research

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Abstract

There are studies showing that parenteral nutrition fluids used for adaptation of preterm infants contain aluminum. It is known that aluminum accumulates in the body, disrupts mental development, affects bone mineral structure. In our study, we aimed to investigate parenteral nutrition and aluminum transmission in preterm infants. A total of 45 babies born during pregnancy week ≤ 32 and / or under 1500 gr were included in the study. A statistically significant increase was observed when we compared the levels of aluminum in the cord blood and in the 14th day of the patients. When the factors affecting serum aluminum levels were examined, no significant difference was found between birth weight, birth week and gender. No statistically significant difference was found between the duration of taking antibiotics, inotropic drugs serum aluminum levels. Statistically significance was found between number of days of furosemid administration and serum Al levels. Longer parenteral nutrition was associated with greater increase in serum aluminium levels. A significant positive correlation was found between serum aluminium levels on 14th day and the calcium and magnesium levels in the TPN solutions which were administered in the first 7 days. In conclusion, the increase in serum aluminum levels in preterm infants fed parenteral nutrition was found to be statistically significant. In infants with longer parenteral nutrition, the increase in serum aluminum levels was greater. It is planned to continue our research in terms of long term effects of aluminum.

Introduction

Ensuring the survival of preterm infants depends on nutrition, and thus, total parenteral nutrition must be viewed as a cornerstone particularly in the treatment of babies born under 32 gestational weeks. Today, all the authors define TPN (total parenteral nutrition) as an indispensable method for ensuring the growth and development of infants (1). Is aluminum toxicity an unrecognized side effect of TPN? Aluminum toxicity was first described by Sedman et al. in 1985 in premature infants receiving parenteral nutrition (2). When aluminum is administered intravenously, it bypasses the gastrointestinal control mechanism, and excessive intake results in tissue accumulation. Due to accumulation, findings of aluminum toxicity that may affect several systems are observed. The limited number of studies has shown that, in the long term, clinical findings such as encephalopathy, impairments in neurological development, bone pain, osteopenia, osteomalacia, microcytic anemia, and cholelithiasis are observed in preterm babies (3,4).

Metabolism of aluminum in preterm infants remains unclear. It has been shown that blood and urine aluminum levels are increased in premature infants receiving parenteral nutrition (2,5). According to the United States Food and Drug Administration recommendations issued in January 2000, daily aluminum intake limit in Total Parenteral Nutrition fluid is set to $5\mu\text{g/kg/d}$ for the neonatal period. Several studies have demonstrated that calcium gluconate, trace elements, phosphate salts and vitamin solutions used in neonatal parenteral nutrition are one of the most important sources of aluminum contamination (8,9). It has been indicated that, in preterm infants on TPN containing a high amount of aluminum, 18 months BMC (bone mineral content) scores are impacted negatively (4), the amount of aluminum has a negative

impact on lumbar bone density in long-term follow-up, and osteoporosis and hip fracture may occur during adolescence.

There is a lack of available studies to conclude aluminum exposure in premature infants. Our study aims to investigate the hypothesis that aluminum levels are significantly increased in premature infants with longer exposure to TPN with less than 32 weeks of gestation.

Methods

Our study was designed as a single-center prospective study. All infants born and treated in our clinic with ≤ 32 gestational weeks and/or birth weight < 1500 grams were included in the study. A cord blood sample was collected from all of the infants at birth. At the end of the first 14 days in the clinic, infants receiving parenteral nutrition for ≥ 7 days were enrolled in this study. A blood sample was collected via specifically designed tubes (BD Vacutainer® SST™ $\square$ Advance, BD Belliver Industrial, UK). Aluminum levels were compared between cord blood and blood test results of day 14.

Sample Size: A difference between the paired groups with medium effect size was determined as significant and the sample size was calculated with t-test. The sample size was set as 45 with %95 power at 0.05 alpha.

Clinical Data Collection from the Patients

The demographic data recorded for the enrolled infants included the following: gestational age, sex, use of antenatal steroid, early membrane rupture, birth weight, mode of delivery, perinatal asphyxia, length of hospital stay, duration of oxygen therapy and mechanical ventilation and CPAP (continuous positive airway pressure), dopamine, dobutamine, history of antibiotic treatment, respiratory distress syndrome, bronchopulmonary dysplasia, sepsis, diagnosis of necrotizing enterocolitis and intraventricular hemorrhage, the daily amount of parenteral nutrition fluid, content and the total duration of intake. All data was collected daily.

Laboratory Results

For the evaluation of serum aluminum levels, the cord blood sample was collected at birth, and on the 14th day, a blood sample was obtained from the central venous catheter. Hemogram and biochemical parameters were registered on infant records. In infants on TPN, aluminum levels were measured 4 hours after TPN discontinuation. Blood samples collected for aluminum were transferred into gel-free tubes via vacutainer and no other needles or contents were added. Centrifugation was done for 15 minutes and placed in Sarsedt polypropylene tubes via plasma polyethylene pipette. The samples were kept in the cold chain at -80°C . Serum aluminum levels were analyzed via SHIMADZU 7000 Series Atomic Absorption device.

Exclusion criteria:

The exclusion criteria were as follows: infants with gestational age >32 weeks or birth weight >1500 gr, TPN duration <7 days at the first 14 days of life, parents do not give consent to participate in the study, presence of major life-threatening congenital abnormality (cyanotic congenital heart disease, hydrocephalus, genetic syndromes, etc.), infant mortality before the sampling process.

Statistical Analysis

Statistical analysis was conducted with SPSS 15.0 for Windows. Descriptive statistics were presented in number and percentage for categorical variables and mean and standard deviation (SD) for numerical variables. As differences in numerical variables between paired groups do not meet the criteria of the normal distribution, differences were calculated with the Wilcoxon test. Independent samples comparisons were performed with the Mann Whitney U test and multiple group comparisons were performed with Kruskal Wallis Test due to non-normal distributions. Correlational analysis was performed with Spearman Correlation Analysis as parametric test criteria were not met. Alpha level was .05.

Results

In our hospital, 4200 babies were born between November 2016 and March 2018. There were a total of 113 babies with a gestational week $\leq$ 32 weeks and / or below 1500 grams. The study was carried out with 45 infants matching the criteria. The flow chart of the study is presented in Figure 1. The demographic and clinical features of infants included in the study are presented in Table 1.

The contents of parenteral nutrition solutions given to infants during follow-up were recorded as kg/day, and total values, mean values, and SD were calculated and presented in Table 2. When cord blood and 14th day serum aluminum levels were compared, a significant increase was found in 14th day serum aluminum levels (Figure 2). Serum aluminum level was $3,35 \pm 1,73$ $\mu\text{g/L}$ in cord blood, while the 14th day serum aluminum level was found to be $4,79 \pm 3,54$ $\mu\text{g/L}$. The difference between cord blood and 14th day serum aluminum level was determined as $1,44 \pm 3,86$ (0,28-2,60) ($p=0,021$). When the duration of parenteral nutrition and aluminum levels were compared; although the increase was found to be greater in infants receiving parenteral nutrition for more than 7 days, no statistically significant difference was found compared to the infants on parenteral nutrition for 7 days ($p=0,609$) (Figure 3). The results of factors affecting the cord blood and 14th day aluminum levels are presented in Table 3 and 4. It was shown that the amount of calcium and magnesium provided on the 14th day had an impact on serum aluminum levels. A positive correlation was obtained between the amount of calcium and magnesium provided for the first 7 days of life and 14th day serum aluminum levels.

Discussion

TPN support is needed for infants with low birth weight to adapt postnatal life until total enteral feeding is provided. Despite their vital efficacy, parenteral nutrition solutions may result in several complications. One of the potential complications is aluminum toxicity depending on the ingredient. The first study indicating aluminum contamination of parenteral nutrition solutions was published in 1982 (5), and the study conducted by Sedman et al. in 1985 investigated blood, urine, and blood aluminum levels in premature babies to show the effect of aluminum in parenteral solutions. The analysis found significantly high blood, bone, and urine aluminum levels in infants receiving parenteral nutrition (2).

In 1991, the American Society for Clinical Nutrition (ASCN) and American Society for Parenteral and Enteral Nutrition (ASPEN) suggested that the safe level of aluminum in parenteral nutrition solutions is <2 mcg/kg/day (10). As of the update in 2000, aluminum exposure in Total Parenteral Nutrition fluids was divided into two as small-volume parenteral fluids and large-volume parenteral fluids (10).

Following the recommendations of the FDA, the amount of aluminum in parenteral fluids, and the ingredients causing aluminum contamination were investigated based on the compatibility with the recommendations on the amount of aluminum (11,12). It was concluded that calcium solutions were significantly higher in parenteral fluids whose aluminum level was above the FDA recommendation (8). A study conducted by Mouser et al. indicated that aluminum contamination was associated with calcium gluconate by 81%. According to a study conducted in Mexico regarding aluminum contamination, it was found that the main sources of contamination were calcium, phosphate salts, and trace elements. However, plasma aluminum levels were not measured in this study (13). In a study showing that calcium and phosphate salts are the most important aluminum source, calcium salts were compared and recommended that calcium gluconate should not be preferred as it contains high aluminum. In our study, a positive significant correlation was found between the amount of calcium and magnesium in TPN at the first 7 days and 14th day serum aluminum levels. No significant correlation was found between phosphate solution, other parenteral solution ingredients (lipid, protein, sodium, potassium chloride) and serum aluminum levels.

In a study comparing aluminum levels in parenteral fluid with aluminum levels determined by manufacturers; Parenteral fluid samples of 40 patients were examined and compared with the total aluminum content determined by the companies (15). While measured aluminum levels were found to be lower than the levels determined by manufacturers, the highest aluminum intake was shown in infants with a birth weight of <1000 g. The explanation for this is the high level of aluminum in calcium gluconate, where increased calcium needs are provided (15). In another study examining the relationship between birth weight and gestational week and aluminum levels, no significant relationship was found (16). In our study, we did not find a correlation between birth weight and gestation week and serum aluminum values in support of these findings.

In a study conducted with 27 children with a diagnosis of intestinal disease and receive more than 25% of their total calories with parenteral nutrition for over 6 weeks compared with a healthy control group; plasma aluminum level was significantly higher in the group receiving parenteral nutrition (8). It has been

reported that serum aluminum level is 3 to 4 times higher than the level it should be. The same study demonstrated that parenteral fluid volume and infusion time were shown to be effective in increasing serum aluminum levels. The level of aluminum in 10 samples randomly selected from the parenteral solutions of the patients was examined, and it was found to be 3 times higher (mean $15.4 \pm 15 \mu\text{g} / \text{kg} / \text{d}$) than the FDA recommendation (8). In our study, aluminum levels of infants receiving parenteral fluid for 7 days, and more than 7 days were compared. Infants receiving parenteral nutrition for a longer time had higher levels of serum aluminum, however, no statistically significant difference was found. In infants receiving parenteral nutrition for more than 7 days, the aluminum increase was higher ($1,79 \pm 3,94 \mu\text{g/L}$), while it was lower in infants receiving parenteral nutrition for 7 days ($0,49 \pm 2,06 \mu\text{g/L}$). No significant correlation was observed between TPN volume and serum aluminum.

In a study conducted in Brazil in 2009 to examine the aluminum levels of the parenteral fluid contents and drugs used in newborns; The amount of aluminum measured in the dopamine preparation is $695.3 \pm 29 \text{ mcg} / \text{L}$ and the amount of aluminum measured in Dobutamine is $475.2 \pm 105.1 \text{ mcg} / \text{L}$ (17).

Besides, aluminum contamination was increased during dilution (17). In our study patients receiving dopamine and dobutamine for more than 3 days and less than 3 days were compared, however, statistical data could not be obtained due to an insufficient number of patients enrolled. However, in babies who received dopamine or dobutamine treatment for more than 3 days, the rate of increase in serum aluminum level was found to be high on the 14th day of the babies.

Along with the TPN, it is known that medications given to children are one of the sources of aluminum. When aluminum concentration level in drugs was assessed, it was measured $251,5 \pm 22,1 \text{ mcg/L}$ for amikacin, and $164,4 \pm 61,7 \text{ mcg/L}$ for gentamicin (16). In our study, when infants receiving Ampicillin, Gentamicin, Amikacin for less than 7 days, and more than 7 days were compared, no significant difference was found in serum aluminum levels. Aluminum levels measured in furosemide was $54,4 \pm 10,3 \text{ mcg/L}$, while it was measured $1832 \pm 25 \text{ mcg/L}$ in dexamethasone (16). According to our study, the duration of furosemide administration was found to be efficient in increasing aluminum levels, and serum aluminum levels were greater in patients receiving furosemide for more than 3 days.

Limitations

Although our study is the first study to examine serum aluminum levels in premature babies, we acknowledge that there are limitations. First, administered parenteral solutions and the aluminum contents of drugs were not measured simultaneously. Due to the insufficient number of cases enrolled in the study, a sufficient number of subgroups could not be achieved and thus, resulted in a decrease in effect size.

In conclusion, serum aluminum level increases significantly on the 14th day according to cord blood values of preterm babies. In babies who take dopamine, dobutamine and furosemide for more than 3 days in the first 14 days of life, serum aluminum levels increase significantly compared to babies who do not. It should be considered that the total parenteral solution and drugs used to survive preterm babies

are risky in terms of potential aluminum toxicity. The findings suggest that there is a need for further research with large case number and also exploring long-term effects.

Declarations

Informed Consent: Ethical approval for this study was obtained from Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee on 01.11.2016 (1312/2016). Written and verbal consent were obtained from the parents of the infants included in the study.

References

References not available with this version.

Tables

Due to technical limitations, table 1-4 is only available as a download in the Supplemental Files section.

Figures

Image not available with this version

Figure 1

The flow chart of the study is presented in Figure 1.

Image not available with this version

Figure 2

a significant increase was found in 14th day serum aluminum levels (Figure 2).

Image not available with this version

Figure 3

no statistically significant difference was found compared to the infants on parenteral nutrition for 7 days ($p=0,609$) (Figure 3).

Supplementary Files

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- [table.pdf](#)