Journal of Population Therapeutics & Clinical Pharmacology

Impact of Parenteral Amino Acid Intake on Electrolytes Levels Among Preterm Infants: A Retrospective Study

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Abstract:

Parenteral nutrition (PN) is recommended for premature babies weighing less than 1500 g. The administration of high doses of amino acids (AA) immediately after birth is recommended to maintain adequate premature growth and development. However, some studies have suggested that such high AA doses can cause electrolyte imbalance. Therefore, the aim of this study is to identify the correlation between daily AA intake and relative serum electrolyte levels. A retrospective cross-sectional study was conducted comparing two groups of preterm infants born before 34 weeks gestation with birth weights of less than 1500 g managed with PN. 214 infants' records were included in the study: 121 were administered with less than 3 g/kg/day of AA (low-intake group) and 93 were administered at least 3 g/kg/day (high-intake group) throughout seven consecutive days. Serum sodium level was found to be normal in both groups; however, the mean value of patients received ≥ 3 g AA was higher than the patients receiving < 3g AA and this difference was statistically significant (p=0.011). The mean values of serum chloride, phosphate, potassium, magnesium, and calcium have no statistically significant difference between the two groups. Hyperchloremia and hypophosphatemia were observed in both groups. Hypermagnesemia and hypercalcemia were observed in patients receiving < 3 g AA. Thus, there was no association between electrolyte imbalance and the AA dose delivered by PN in the high-intake group of preterm infants.

Keywords: Parenteral amino acid, Preterm infants, Electrolytes level

Introduction

The development and maturation of vital organs during the late gestation period depend mainly on a constant nutritional supply for the fetus [1]. Very low birth weight preterm infants (VLBW) (birth weight <1,500 g) are a high-risk group for postnatal growth restriction due to the premature disruption of nutrient transport across the placenta at a critical time of growth and development [2]. To achieve the optimum fetal growth rates with acceptable functional development, parenteral nutrition (PN) is known to be a well-established approach for preterm infants [3,4,5].

Current clinical studies recommend administering an aggressive regimen of PN to ensure sufficient energy intake through high protein concentrations in combination with maternal breastfeeding [5,6,7]. Although this approach appeared to be effective in optimizing postnatal nutrition and neuro-development, several findings of recent studies reported that a high amino acids (AA) intake (>3g/kg/day) can cause severe electrolyte alterations, specifically calcium and phosphorus metabolism [2,8]. A higher prevalence of hypercalcemia, hypophosphatemia, hypokalemia, and an increased risk of septicemia were noted in VLBW newborns who received AA levels of 3.5 g/kg/day, compared to newborns who received amounts of 2 g/kg/day [9]. Electrolyte disturbances are usually without symptoms. However, hypercalcemia results in vomiting, agitation, and ventricular arrhythmias, while severe hypophosphatemia is associated with weak muscle quality, longer duration of ventilator support and nosocomial infections [8,10]. Yet, some other findings reported no significant associations between high concentrations of AA and electrolyte disturbances [11].

So, there is an urgent need to study and identify the prevalence of high protein concentrations of PN and the development of electrolyte imbalance (hypercalcemia, hypophosphatemia, and hypokalemia) in a retrospective cross-sectional study for preterm infants born less than 34 weeks gestational age with a birth weight less than 1.5 Kg. Consequently, correlating electrolyte imbalances with potential impacts on neonatal development.

Materials and Methods

Study Design: This is a single-site, cross-sectional study in which data from the patient's records were collected from the 1st of January 2020 to the 30th of December 2021 for this study.

Study Setting: The study was conducted at King Salman Military Hospital in Tabuk (the largest hospital in the Tabuk region, providing clinical services for preterm infants with reproducible laboratory analysis and patient registry entry).

Subjects Eligibility Criteria:

Inclusion Criteria: All neonates born before the age of 34 weeks gestation with birth weights of less than 1500 g with regular PN intake for at least 7 consecutive days with available data on their laboratory investigations in their records.

Exclusion Criteria: Any VLBW preterm neonates with PN less than 7 days and infants with major congenital anomalies.

Data Collection Tools: The data were collected using patient registry entry records and laboratory data.

Outcome Measurements: Patient demographics, nutritional intake categorized according to the amount of AA intake above or below 3g/kg of protein intake [12], birth weight, and electrolyte plasma concentration.

Statistical Analysis: All the data were collected using Excel software. SPSS statistical subroutines were used for statistical analysis. The t-test (for continuous outcomes) and chi-square test (for binary outcomes) were employed in the analysis, and a level

of significance equal to 0.05 for the present study was considered significant.

Ethical Consideration: Data were collected after obtaining ethical approval from the Institutional Research Review Board (IRB) of ISNC-RC with an approval code (KSAFH-REC-2021-435). The confidentiality of the anonymously collected data was maintained all the time. All the data was stored in a secure and safe place, only accessible by the researcher.

Results

Characteristics of the Study Population

Based on the inclusion and exclusion criteria, this study included 214 preterm infants treated with PN. The preterm infants were classified into two groups: patients receiving AA < 3g (n=121) and ≥ 3g (n=93). Table (1) represents the characteristics of the study population, with predominant male gender among both groups; however, the distribution of gender has no statistical significance (p=0.384) in the study population. Similarly, the distribution of gestational age also has no statistical significance between the two groups (p=0.120). The mean body weight of the patients who received AA <3g was significantly (p=0.01) higher than the patients who received AA ≥3g. Respiratory distress was found to be the most common complication, which was higher among the patients who received AA <3g with a statistically significant difference (p=0.023). There was no any statistical significant difference between both groups with respect to the intrauterine growth restriction (p=0.452) and both groups showed sepsis in some cases with no statistical significance too (p=0.672). Moreover, both groups showed no statistical significant difference regarding other complications such as bladder exstrophy, congenital diaphragmatic hernia, oesophageal Atresia, tracheoesophageal fistula, necrotizing enterocolitis and atrial septal disease.

Characteristics of Nutritional Intake Among the Study Population

Student t-test was used to test the statistical significance between the two groups regarding the characteristics of nutrition delivered (Table 2). Mean total expressed breast milk (EBM) calories and feeds volume were found to be higher in patients who received AA < 3g and this difference was statistically significant; however, total fluid intake in 24 hours, total PN volume, total calories from PN, total calories from all sources, dextrose, potassium, calcium gluconate, amino acids and lipids from all sources were higher in patient who received AA ≥ 3g and mean difference was found to be statistically significant. The mean intake of sodium, phosphate, and magnesium sulphate between the two groups had no significant statistical difference.

Serum Electrolytes

Table (3) reveals the mean (SD) difference between the two groups with the statistical association by using the student t-test. Serum sodium level was found to be normal in both groups; however, the mean value of patients who received ≥ 3 g AA was higher than the patients who received < 3 g AA and this difference was statistically significant (p=0.011). Hyperchloremia and hypophosphatemia were observed in both groups. Hypermagnesemia and hypercalcemia were observed in patients who received < 3 g AA. However, the mean value has no significant statistical difference between the two groups for the serum potassium, chloride, magnesium, phosphate, and calcium.

Discussion

Interruption of continuous placental nutritional flow after birth increases the risk of nutrient deficiency in extremely low-birth-weight infants (ELBWIs). The recent Cochrane database systematic reviews on AA supplementation on PN in newborns and the ESPGHAN/ESPEN/ESPR/CSPEN guidelines

recommended starting feeding as soon as possible after birth by AA supplementation with high energy intake and high AA [13,14,15]. The recent introduction of an early aggressive PN in ELBWIs was believed to prevent early inadequate nutrition–induced metabolic disturbances such as hyperphosphatemia, hypocalcemia, non-oliguric hyperkalemia, and hypoglycemia

Table 1: Characteristics of the patients with high and low amino acid intake

Perinatal variables		Patients received < 3 g/Kg of protein (n=121)	Patients received ≥ 3 g/Kg of protein (n=93)	p-value
Male gender	N (%)	67 (55.37)	57 (61.29)	0.384
Gestational age (weeks)	Mean (SD)	30.19 (3.35)	29.52 (2.80)	0.120
Birth weight (Kg)	Mean (SD)	1.28 (0.36)	1.12 (0.28)	0.01*
Respiratory distress	N (%)	99 (81.81)	86 (92.47)	0.023*
Sepsis	N (%)	17 (14.04)	15 (16.12)	0.672
Intrauterine growth restriction	N (%)	3 (2.47)	1 (1.07)	0.452
Others:				
Bladder exstrophy				
Congenital diaphragmatic hernia				
Oesophageal Atresia	N (%)	4 (3.3)	3 (3.22)	0.973
Tracheoesophageal Fistula				
Necrotizing enterocolitis				
Atrial septal disease				

Student t-test was considered to test the statistical significance ($p<0.05$) with mean (SD) between the two groups. The chi-square test was considered to test the statistical significance ($p<0.05$) with N (%) between the two groups. The (*) indicates a statistically significant difference.

Table 2: Characteristics of nutrition delivered among the two groups

Variable		Patients received < 3 g/Kg of protein (n= 121)	Patients received ≥ 3 g/Kg of protein (n=93)	p-value
Total Fluid Intake in 24 hours	Mean (SD)	119.27 (12.32)	122.64 (11.03)	0.029*
Total Calories of EBM	Mean (SD)	3.78 (7.50)	1.44 (3.56)	0.006*
Feeds (EBM) volume	Mean (SD)	8.97 (14.42)	3.93 (7.18)	0.002*
Total PN Volume	Mean (SD)	106.11 (16.32)	116.5 (14.17)	0.000*
Dextrose	Mean (SD)	9.94 (1.27)	11.06 (1.22)	0.000*
Sodium	Mean (SD)	0.94 (0.83)	1.04 (0.88)	0.426
Potassium	Mean (SD)	0.63 (0.36)	0.94 (0.54)	0.000*
Calcium Gluconate	Mean (SD)	0.59 (0.67)	0.67 (0.26)	0.010*

Phosphate	Mean (SD)	0.33 (0.26)	0.41 (0.33)	0.059
Magnesium Sulphate	Mean (SD)	0.069 (0.05)	0.069 (0.05)	0.641
Amino Acid	Mean (SD)	2.59 (0.28)	3.13(0.15)	0.000*
Lipids	Mean (SD)	2.50(0.53)	2.77(0.38)	0.000*
Total Calories From PN	Mean (SD)	58.84 (7.46)	65.41 (5.94)	0.000*
Total Calories from All Sources	Mean (SD)	62.62 (9.36)	66.85 (6.72)	0.000*

Student t-test was considered to test the statistical significance ($p<0.05$) with mean (SD) between the two groups, the (*) indicates a statistically significant difference.

Table 3: Mean sodium, potassium, chloride, magnesium, phosphate and calcium levels for both low and high intake groups in mmol/L.

Variable		**Patients received < 3 g/Kg of protein (n= 121)**	**Patients received ≥ 3 g/Kg of protein (n=93)**	**p-value**
Sodium	Mean (SD)	137.36(5.64)	139.27(4.70)	0.011*****
Potassium	Mean (SD)	5.49(7.10)	4.48(0.50)	0.171
Chloride	Mean (SD)	107.59(7.07)	109.38(6.48)	0.058
Magnesium	Mean (SD)	1.47(7.39)	0.80(0.30)	0.382
Phosphate	Mean (SD)	2.68(7.49)	1.88(2.25)	0.321
Calcium	Mean (SD)	3.13(2.38)	2.38(0.20)	0.329

Student t-test was considered to test the statistical significance ($p<0.05$) with mean (SD) between the two groups, the (*) indicates a statistically significant difference.

by inhibiting cellular catabolism and promoting growth [13]. On the contrary, other publications revealed contradictory results concerning metabolic disturbances that may cause the refeeding-like syndrome. They postulated that this group of imbalances in electrolyte levels is triggered by the abrupt administration of intravenous AA and glucose subsequent to insufficient nourishment. These periods are seen in cases of placental insufficiency or inadequate intravenous intake of energy and protein during the initial days after birth [11,16]. Therefore, the current study was set up to analyse the impact of AA intake on electrolyte levels in preterm infants.

One of the features affected by the amount of AA intake was the birth weight. In line with a previous randomized clinical trial (RCT), a significant disparity in weight loss was observed between the group that consumed high amounts of AA compared to the control group, as evidenced by a statistically significant p-value of (0.01) [17]. A recent systematic review and meta-analysis reported that a potential explanation for the lack of enhanced growth outcomes could be attributed to the fact that the given AA possessed suboptimal compositions that did not meet the requirements of preterm infants. In addition, the available information regarding the parenteral AA compositions utilized in the various randomized controlled trials was quite limited [18].

In our study the serum sodium level was found to be normal in both groups; however, the mean value of patients who received ≥ 3 g AA was higher than the patients who received <3g AA with a statistically significant difference (p=0.011). On the contrary, Bonsante et al. demonstrated that natremia was not influenced by AA intake [19]. Sodium (Na) balance was largely negative in each group during the first days of life. It was strongly associated with postnatal age and urine output, with very little effect on GA and AA intake. Our data confirmed that a negative Na balance is a necessary event after birth, closely

linked to extracellular water volume and weight loss, and is slightly modulated by a nutritional approach [19].

Moreover, the relationship between total body potassium (K) and protein content is well-established in the preterm baby [20]. The findings showed that patients receiving <3g or ≥ 3 g/kg AA had normal potassium levels with no statistically significant difference between groups (p-value=0.171). Our results contradict what was reported in a past trial which clarified that high and early AA intake may prevent hyperkaliemia and enhance potassium levels [21]. This can be justified by the movement of the element from the intracellular space to the extracellular space (plasma). Also, it can be attributed to a decrease in the sodium-potassium adenosine triphosphatase (ATPase) activity and the limited elimination of potassium through the kidneys [22].

Phosphate is another equally important electrolyte as K that plays a crucial role in several metabolic processes and is essential for some cell functions. Unfortunately, preterm infants are born with low levels of phosphate. As a result, it was recommended to administer early and high micro-nutrients intakes through parenteral means. However, this study, along with other similar studies, observed hypophosphatemia with no significant difference in the amount of protein intake through PN (p-value=0.321) [13,23].

Further studies have postulated different hypotheses for this observation. The refeeding-like syndrome was thought to lower the serum phosphate level, which was previously described [24]. An alternative hypothesis posits that early postnatal hypophosphatemia can be attributed to a condition known as "placental incompletely restored feeding syndrome". According to this particular theory, preterm infants experience an insufficiency of essential nutrients, specifically phosphate, despite receiving an adequate supply of calories and AA. Consequently, this nutrient deficiency results in a reduced level of serum phosphate among these infants [25].

According to Parramón-Teixidó, the frequency of moderate hypophosphatemia (<1.1 mmol/L) was 21.7% (13/60 patients) in the low-intake group and 27.8% (15/54 patients) in the high-intake group [11]. Also, Brener et al. found that 58.3% (35/60) of patients who received 3 to 3.5 g/kg/day of AA developed moderate hypophosphatemia [11,26]. Last of all, they concluded that severe hypophosphatemia (<0.9 mmol/L), which can be clinically relevant, was in 11.7% (7/60) of patients in the low-intake group and in 9.3% (5/54) of patients in the high-intake group [11].

On the contrary, a trial showed that the deficit phosphate intake (estimated requirement–actual intake) during the first 5 days before the nadir of hypophosphatemia was higher in period II (high intake) than in period I (low intake) (2.6 ± 1.3 versus 4.0 ± 1.3 mM/kg/day, $p < 0.01$). Because there was no difference in the phosphate intake between the two periods, the increased cumulative deficit in period II (high intake) might be a result of an increased estimated requirement of phosphate due to augmented AA anabolism. The lower phosphate supply since birth, combined with a scarce deposition of minerals in the bone and higher protein anabolism, led to early hypophosphatemia, which was severe in the undernourished SGA infants. Thus, the optimal amounts for AA and phosphate intake in high-risk infants remain unclear [13].

Furthermore, it was identified that the patients receiving <3g AA suffered from hypercalcemia with no statistically significant difference between the two groups (p-value=0.329). On the other hand, a group of researchers confirmed the incidence of

hypercalcemia in the higher AA group [27]. In addition, Brener et al. exhibited a similar proportion of 87% (35/40) in patients given higher doses of AA [26]. A possible justification was due to the potential hazard of premature disturbances in mineral levels while administering "early aggressive" nourishment and delaying the provision of phosphorus until the second and third days after birth [28].

On the other hand, Parramón-Teixidó found a similar prevalence of hypercalcemia in preterm infants managed with PN that received at least 3 g/kg/day of AA (high-intake group) and those that received doses of less than 3 g/kg/day (low-intake group). It was also explained that the total and ionized calcium plasma levels vary in relation to albumin levels, which are generally low in preterm infants [11].

A strong relationship between calcium and phosphorus has been identified since they are both responsible for the growth of the human skeleton. For that reason, a compelling recommendation is to employ a molar calcium-to-phosphorus ratio that is below 1.0 (ranging from 0.8 to 1.0) with the intention of diminishing the occurrence of early postnatal hypercalcemia and hypophosphatemia [29].

Moreover, ESPGHAN/ESPEN/ESPR/CSPEN recommended giving at least 1.5 g/kg/day of AA intake on the first day, as soon as possible after birth to fulfill an anabolic state. In addition, from the second postnatal day onwards, the recommended amount of AA should range between 2.5 g/kg/d and 3.5 g/kg/d. It is also advised that this intake be supplemented with non-protein intakes exceeding 65 kcal/kg/d, along with sufficient micro-nutrient intakes [14].

Conclusion

Within the limitations of the retrospective nature of the study, the recommended high intake of amino acids (≥ 3 g/Kg) does not cause electrolyte imbalance (hypercalcemia, hypophosphatemia, or hypokalaemia) in very low birth weight preterm infants (<1500 g).

Conflict of Interest: No conflict of interest was found between the authors and any other organization or company

Authors Contributions: A.A. did the practical work, drafted this manuscript, and participated in developing the research idea. I.A. and M.A. participated in data collection and writing the manuscript. F.A. performed the statistical analysis. K.A. supervised all the practical work, lead the conceptualization of the idea. All authors revised the final form of the manuscript critically.

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