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Original Research Paper

Neonatology

THE IMPACT OF AGGRESSIVE PARENTERAL AMINO ACID ADMINISTRATION ON BLOOD UREA NITROGEN LEVEL IN PRETERM NEONATES

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ABSTRACT

Conventional parenteral amino acid for preterm neonate is initiated in several days after birth with a low starting dose. It is caused by a concern regarding the elevation of Blood Urea Nitrogen (BUN) from aggressive amino acid administration. It causes negative nitrogen balance and impairs growth and development of the neonate.

Objective: To determine the impact of aggressive parenteral amino acid administration on BUN level in preterm neonates.

Method: A total of 38 subjects were enrolled in this study based on inclusion and exclusion criteria. Subjects were randomized into control and intervention groups. Control and intervention groups received parenteral amino acid at starting dose of 1.5 g/kgBW/day and 3 g/kgBW/day, respectively, which were increased gradually in 3 days. BUN level was measure on the first and third day. Data was analyzed using computer software and p value of <0.05 was considered significant.

Results: Higher BUN level was observed in control group (10.4 mg/mL) compared to intervention group (8.2 mg/mL). Weight increment was more prominent in intervention group (20 g) compared to control group (0 g). There was no significant association between the method of amino acid administration and BUN level ($p = 0.562$). There was no significant correlation between total amino acid intake and BUN level ($p = 0.108$).

Conclusion: There is no impact of aggressive parenteral amino acid administration on BUN level in this study.

KEYWORDS : blood urea nitrogen, parenteral amino acid, preterm neonate

INTRODUCTION

Parenteral nutrition is the administration of required nutrients for growth and metabolism via intravenous route. The goal of nutritional administration is to achieve optimal postnatal growth despite various patient conditions. For neonates, parenteral nutrition is indicated in several cases includes prematurity (Rao., 2015). Preterm neonate is neonate born before gestational age of 37 weeks (Kadim et al.,2016). The prevalence of preterm birth is approximately between 5% to 18% of all life births and about 85% is occurred in Asian and African regions (Shah et al., 2104). Indonesia is in the fifth place of the most prevalence preterm birth country list with annual preterm birth of 675 700(Kadim et al.,2016).

Preterm neonate fails to gain postnatal optimal growth due to several medical problems such as respiratory distress (Ho M at al., 2016). One of the many factors which influences the condition is inadequate nutritional administration (Liu et al., 2015).Respiratory distress, which is caused by immaturity and surfactant deficiency in preterm neonate, will create hypoxemia condition, trigger anaerobic metabolism, and increase the risk of necrotizing enterocolitis which worsen the nutritional status (Ho M at al., 2016).

Some experts agreed that aggressive nutritional administration, particularly amino acid, may prevent the conditions above (Hay., 2013). Aggressive nutritional administration is the initiation of nutritional intake within the first 24 hours of life via enteral or parenteral route with higher amount of nutrients. In aggressive nutritional administration, amino acid is given at a starting dose of 3 g/kgBW/day[1] compared to 1.5 g/kgBW/day in conventional one. High protein intake plays important role in reaching positive nitrogen balance and thus prevent post natal growth failure in preterm neonate (Kadim et al., 2016).

This study is aimed to determine the impact of aggressive parenteral amino acid administration on hypoxia-induced nitrogen balance.

METHODS

A randomized experimental clinical trial was conducted in H. Adam Malik Hospital from September to December 2018. Subjects were preterm neonates receiving parenteral amino acid. Subjects with congenital or acquired renal and liver disorders, and who was discharged on parental or relative's will before receiving parenteral amino acid for 3 days were excluded. Informed consent was obtained from each subject's parent or relative. Subjects were randomized using simple random sampling into control and intervention groups. Control group received conventional amino acid administration (starting dose of 1.5 g/kgBW/day then increased 0.5 g/kgBW/day for 3 days) and intervention group received aggressive amino acid administration (starting dose of 3 g/kgBW/day then increased 0.5 g/kgBW/day for 3 days). Demographic data was collected before the intervention started. Blood urea nitrogen (BUN) as the surrogate measurement nitrogen balance was measured before amino acid administration and 3 days after the intervention. Body weight was also measured in 3 days after amino acid administration. Statistical analysis was done using computer software (Statistical Package for Social Science – SPSS) at 95% confidence interval. P value of <0.05 was considered significant. We used T independent test to determine the impact of aggressive amino acid administration on BUN level. Pearson correlation test were used to analyze the impact of total amino acid administration on BUN level. This study had been approved by the Research Ethical Committee, Medical School, Universitas Sumatera Utara.

RESULTS

A total of 38 neonates were enrolled in this study. All of them were randomized into control and intervention groups (19 neonates in each group). Male subjects with >32 weeks of gestational age were dominant. Median chronological age in both groups was not different. Median weight increment in intervention group was higher that control group. Higher BUN level was observed in control group (Table 1).

Table 1. Baseline characteristic of subjects

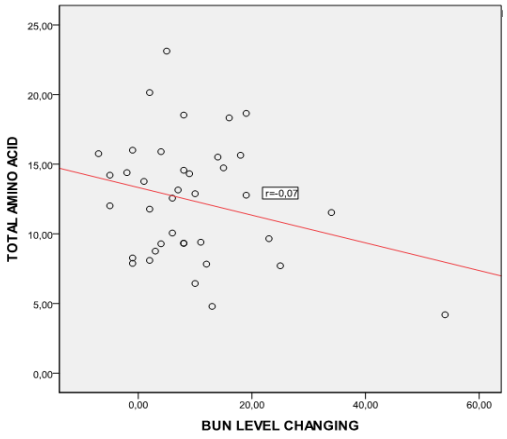
Characteristics	Control n=19	Intervention n=19
Sex, n(%) Male Female	9 (47.4) 10 (52.6)	13 (68.4) 6 (31.6)
Gestational age, n (%) <32 weeks ≥32 weeks	14 (73.7) 5 (26.3)	9 (47.4) 10 (52.6)
Median chronological age, day (min-max)	1 (1-2)	1 (1-2)
Mean 1st day weight, gram (SD)	1603.9 (511.43)	1439.2 (333.29)
Mean 3rd day weight (SD)	1597.1 (504.23)	1455.2 (339.08)
Mean total amino acid, gram (SD)	9.5 (3.03)	15.2 (3.50)
Mean 1st day BUN, mg/dL (SD)	17.3 (8.98)	17.8 (7.93)
Median 3rd day BUN, mg/dL (min-max)	27 (11-78)	25.0 (10-45)
Mean BUN level changing, mg/dL (SD)	10.4 (14.76)	8.2 (7.29)

We observed no impact of aggressive amino acid administration on BUN level (p=0.562) and weight increment (p=0.127). Mean BUN level changing in control group was 10.4 mg/dL vs 8.2 mg/dL in intervention group. Total amino acid administered had no impact on BUN level changing (p=0.108) and weight increment (p=0.243) (Table 2).

Table 2. The impact of total amino acid on BUN level and body weight

	Control group	Intervention group	r	Nilai p
Mean total amino acid, gram (SB)	9.5 (3.03)	15.2 (3.50)	-0.265	0.108
Mean BUN level changing,mg/dL (SB)	10.4 (14.76)	8.2 (7.29)		

Pearson correlation test



DISCUSSION

Approximately 11.1% of total life births worldwide were premature (Pignotti et al., 2015). The incidence of prematurity is increasing. In Europe, its incidence is 5% to 9% of all births, while in USA the incidence is 12% (Kaczmarczyk et al., 2017). Preterm birth is more frequent in male compared to female with percentage of 55% vs 45% (Blencowe et al., 2013). In this study, 57.9% subjects were male.

Preterm neonate generally has low birth weight (Pignotti et al., 2015). Preterm neonate also has several life threatening conditions such as hyaline membrane disease, bronchopulmonary dysplasia, *apnea of prematurity,* persistent ductus arteriosus, hypothermia, hyperglycemia, hypocalcemia, retinopathy of prematurity, and immature digestive function (Carlo., 2016). In this study, mean 1st day body weight in intervention group was 1 439.2 grams while in control group was 1 603.9 grams.

The above conditions will induce metabolic stress and inflammation from cytokines release and trigger catabolic state. During catabolic state, body's energy storage will be sused to fulfill the increasing energy need (de Boo et al., 2007). Management of preterm neonate will also worsen the catabolic state. Repeated blood sampling may cause iatrogenic anemia. Ventilator and catecholamine usage will increase energy need. Antibiotic administration may disturb normal flora balance in the gut (Hay et al., 2013).

Conventionally, parenteral amino acid is administered at starting dose of 1.5 g/kgBW/day several day after birth while in aggressive administration, the initial dose is 3 g/kgBW/day directly after birth. In both methods, the dose is increased gradually to maximum dose of 4 g/kgBW/day (Ho M et al., 2016). Higher amino acid will give positive impact toward nitrogen balance. Protein which is administered will prevent body's protein catabolism because energy and homeostasis requirement are met. The rest of protein will be stored as protein deposit which marks the shift from katabolic to anabolic state (de Boo et al., 2007).

In this study, we randomized subjects into control and intervention groups. In control group, we gave parenteral amino acid with initial dose of 1.5-2.5 g/kgBW/day while in intervention group we started parenteral amino acid at dose of 3 g/kgBW/day. The amount of amino acid was increased at a rate of 0.5 g/kgBW/day to maximum dose of 4 g/kgBW/day.

Another study reported that physical growth of neonate in the first 3 weeks of life was associated with the amount of administered amino acid. Higher amino acid administration would give better neonate's physical growth (Weintraub et al., 2015).A study by Torer, et al found that there was no difference in weight increment between neonate receiving 2.5 g/kgBW/day of amino acid compared to neonate receiving 3.5 g/kgBW/day (Törer et al., 2015). This result is in line with our study. We found no association between weight increment and aggressive amino acid administration. This is caused by the fact that our observation was only for 3 days which was within the physiological period where neonate loss 10% to 15% of its birth weight (Su B., 2014).

Previous literatures stated that parenteral amino acid administration may cause hyperammonemia, and azotemia from BUN level increasing, and metabolic acidosis in preterm neonate (Dounousi et al., 2015). This is caused by nitrogen metabolism from amino acid breakdown which produce ammonia and metabolized in the liver to form urea. In preterm neonate, there is a theory that liver function is still immature and can make elevated blood ammonia level (de Boo et al., 2007). Urea as the end metabolic product will be eliminated from kidney. Some literatures stated that preterm neonate has impaired renal function so the urea can't be excreted. This is marked by elevated plasma BUN level which is also known as azotemia (Ridout et all., 2005). Metabolic acidosis may happen from cationic amino acid metabolism (arginin, lysin, dan histidin) and amino acid containing sulfuric acid metabolism (methionin, cystein, dan cystin) which produce hydrogen ion and sulfuric acid. High anion gap acidosis metabolic will be found (Dounousi et al.,2015).

In our study, there was no association between amino acid administration with BUN level. This implied that aggressive amino acid administration with starting dose of 3 g/kgBW/day which was increased to a maximum dose of 4 g/kgBW/day was safe and did not induce significant adverse effect in preterm neonate. Our study is supported by several previous

studies. Ridout, et al reported that BUN level was not associated with amino acid administration in preterm neonate (Ridout et all., 2005). Weintraub, et al stated that the limitation of amino acid administration up to 4 g/kgBW/day did not give beneficial impact on neonate (Weintraub et al., 2015). A study by Ibrahim, et al showed that aggressive amino acid administration would give positive nitrogen balance without significant metabolic acidosis and BUN level changing (Ibrahim et al., 2004).

This study has several limitations. First, the observation period in this study was only 3 days and this may mask the impact of aggressive amino acid on weight increment. Second, subjects in this study was not fully from <32 weeks of gestational age which was the obligate candidate for parenteral amino acid recipient. From this study we can conclude that there is no impact of aggressive parenteral amino acid administration on BUN level.

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