Medical Science and Discovery
ISSN: 2148-6832

Early high dose versus low dose parenteral amino acids administration in the preterm infants: A meta-analysis

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ABSTRACT

Objective: Preterm infants may face difficulty on getting the nutrition required for growth due to incompetence of sucking and immaturity of the gastrointestinal. Preterm infants require higher amounts of amino acids and protein to support the growth of lean body mass and tissue. Administrating amino acid supplementation during the first hour of life is the key to preventing early neonatal malnutrition and can be beneficial in the growth of the neonates.

Objectives: Aim of this study is to determine the effects of early high dose parenteral amino acids administration versus low dose in preterm infants from all collected studies.

Methods: This is a meta-analysis study that studies were collected MedLine, PubMed, and Cochrane Central Register of Controlled Trials comparing early high dose parenteral amino acids versus low dose. High-quality studies, as assessed by Jadad Criteria, were used to evaluate outcomes such as anthropometric data, length of hospital stays, and morbidities.

Results: A total of 9 Randomized controlled trials (RCTs) with total of 960 participants were included in the analysis. Analysis of these studies showed a statistically significant reduction in the time to regain birth weight in the group of early high-dose amino acids administration in the preterm infants. Reductions were 0.79 day (MD 0.79 day, 95% CI 0.06 to 1.52 day; participants = 655; studies = 6; I2 = 0%) (P= 0.03). It also showed a statistically significant reduction in the length of stay with a reduction of 2.09 days in the early high-dose parenteral amino acids groups (MD 2.09 days, 95% CI 1.01 to 3.17 day; participants = 500; studies = 5; I2 = 0%) (P= 0.0002). No significant difference in morbidity of each group was found.

Conclusion: Administration of early high-dose amino acids reduced the time to regain birth weight and the length of hospitalization in preterm infants. The analysis did not show any significant increase in the risk of morbidity.

Keywords: amino acids, protein, parenteral nutrition, preterm infant, neonates

Review Article

Received 14-06-2022

Accepted 25-06-2022

Available Online: 29-06-2022

Published 30-06-2022

INTRODUCTION

Preterm infants may face difficulty on getting the nutrition required for growth due to incompetence of sucking and immaturity of the gastrointestinal that can affect the digestion and absorption function of the complex nutrients (1,2). Full catch-up to the normal rate of growth in preterm infants usually does not occur, and it takes a mean of 14-17 days to regain birth weight in infants of less than 1000 grams upon birth (2,3). In the early days to weeks of life, very-low-birth-weight infants are characterized to have a significant weight loss. The significant weight loss may occur due to ongoing catabolic illness and insufficient protein-energy supply. The other most common causes are mechanical ventilation and high oxygen concentrations that can cause pulmonary and systemic inflammatory processes and contribute to significant weight loss in preterm infants (2).

Extremely-low-birth-weight infants receiving only carbohydrates as a substrate can lose up to 0.6 to 1.1 grams of protein per kilogram per day. In the study conducted by Ho et al., they found that preterm infants who only received intravenous glucose administration will lose about 1% of protein stores daily. The energy obtained from intravenous glucose administration was found to be converted mostly into body fat instead of producing more muscles or bones (3,4)

Earlier and higher nutritional support, particularly amino acids and protein, become more crucial to improve growth and neurodevelopmental outcomes in preterm infants. For this goal, parenteral administration is often used (1,5). Complementation of amino acids has been shown to ameliorate protein balance. This may be caused by increasing protein synthesis that may result on improve in the antioxidant defense system and may potentially prevent a catabolic state and neonatal growth retardation (6). Administrating amino acid supplementation during the first hour of life is the key to preventing the period of early neonatal malnutrition (2).

To date, there has been no agreed consensus yet in the term of optimal starting dose and rate of advancement of parenteral amino acids in preterm infants. Our institution has no exact protocol yet to start parenteral amino acids in preterm infants. The common practice in our institution for giving parenteral amino acids in preterm infants started on the 3rd day of life with the initial dose of 3 g/kg/day. Hence, the aim of this study is to do a thorough study comparing the effects of high dose to low dose early parenteral amino acids administration in the preterm infant by analyzing the available researches that have been conducted. The result of this study may be used as a basis of the protocol in giving parenteral amino acids to preterm infants born in the institution.

MATERIAL and METHODS

Eligibility Criteria

Types of Studies

Only RCTs were included in this study. All the RCTs published within the past 10 years were included (2010-2020).

Population of the Study

Preterm infants who were admitted to a neonatal intensive care unit (NICU) and received parenteral amino acids within the first day of life were subjected to the study. The included study sites should be different in location to avoid any duplication of subjects. Studies that included infants with congenital anomalies were excluded.

Intervention and Comparison

The intervention of this study was a higher dose of amino acids administration (≥3.0g/kg/day) versus a lower dose (<3.0g/kg/day).

Outcome of the Study

The primary efficacy outcomes were anthropometric data (time to regain birth weight, body length gain, and head circumference gain) and length of hospital stay. The secondary safety outcomes were the possible morbidities such as sepsis, intraventricular hemorrhage, patent ductus arteriosus, necrotizing enterocolitis, retinopathy of prematurity, and bronchopulmonary dysplasia.

Study Selection

This meta-analysis study was assessed based on the PRISMA guidelines (http://www.prisma-statement.org). The literature search was conducted in MedLine, PubMed, and Cochrane Central Register of Controlled Trials using terms such as "amino acid", "parenteral", "intravenous", "preterm", "very low birth weight", "infant", and "neonate". The included studies were limited to only RCTs, those published in the past 10 years, with English text studies, and available as full text. The RCTs were assessed using the Jadad Criteria (a 0- to 5-point rating scale). The interpretation of score 0-2 is a low-quality study, and score 3-5 is a high-quality study. Only high-quality studies were included in this study.

Data Extraction

Identified studies were reviewed by two independent reviewers (HMP and SZR) to assess the quality of the study, inclusion and exclusion criteria for the study to be included in the analysis.

The following study data were extracted from the studies includes:

1. Title, first author, journal, and year of publication of the studies
2. Study design and study populations' characteristics (total population, gestational age, birth weight), and inclusion and exclusion criteria of each study.
3. The type of intervention done and control (initial dose of amino acids administration given, duration, and start of amino-acid administration)
4. Outcome measures:
   a. Primary efficacy outcomes: anthropometric data (time to regain birth weight, body length gain, and head circumference gain) and length of hospital stay
   b. Secondary safety outcomes: morbidities such as sepsis, intraventricular hemorrhage, patent ductus arteriosus, necrotizing enterocolitis, retinopathy of prematurity, and bronchopulmonary dysplasia.

Statistical Analysis: After all data were collected, statistical analysis was plotted using Review Manager software version 5.3. Categorical outcomes were calculated using Mantel-Haenszel method and the inverse variance method was used for continuous outcomes.

RESULTS

A hundred and seventy-one potentially relevant titles and abstracts were screened in the databases and 137 articles were excluded. The remaining 34 full-text articles were then assessed for eligibility. Of these articles, 9 RCTs met the inclusion criteria (**Figure 1**). Included studies were published between 2010 and 2020.

In the included studies, there were 960 participants, with a total of 480 participants assigned on the intervention group (high dose amino acids) and 480 (low dose amino acids) on the control group. The gestational age of the participants ranges from 24 weeks to 34 weeks AOG. The birth weight ranges from 400 grams to less than 1250 grams were included in the studies. There were two studies by Bulbul et al. (2012) and Can et al. (2012) that did not report the absolute number of the birth weight and instead reported it as appropriate for gestational age. All included studies have a starting dose of intravenous amino acids of ≥ 3 g/kg/day in their high dose amino acid group and a dose of intravenous amino acids of < 3 g/kg/day in their low dose amino acid group. The summary of the characteristics included studies was shown in **Table 1**.

http://dx.doi.org/10.36472/msd.v9i6.755

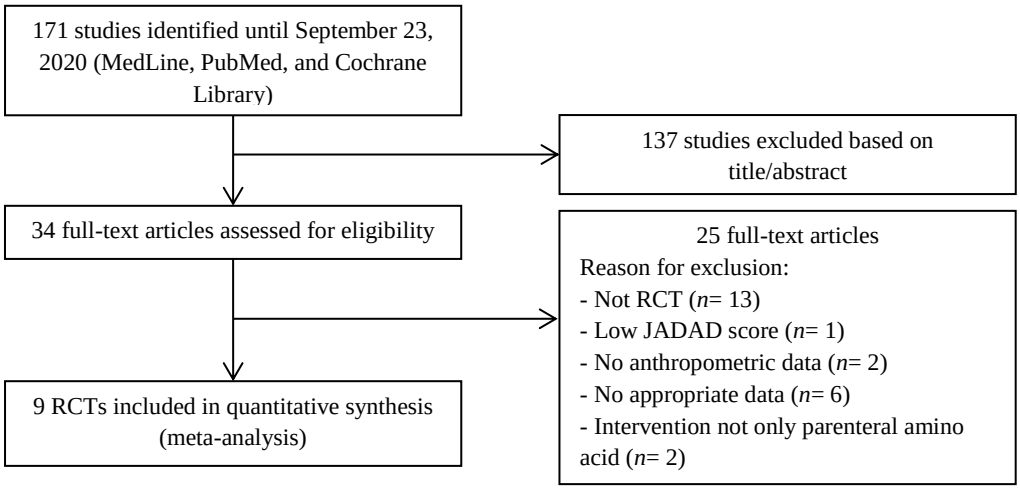

Figure 1. Flow diagram showing the results of the literature search and selection process throughout the study. RCT, Randomized Controlled Trial.

Table 1. Characteristics of included studies[1]

First author, year of publication	Study type	Number of subjects		Gestational age (weeks)	Birth weight (grams)	Study quality
		High AA	Low AA			
Balakrishnan, 2017 [7]	RCT	85	83	24 0/7 – 30 6/7	400 – 1,250	5
Bellagamba, 2016 [8]	RCT	82	82	26 – 29	500 – 1,249	5
Balasubramanian, 2013 [9]	RCT	60	63	29 – 34	900 – 1,250	5
Burrattini, 2013 [10]	RCT	56	58	26 – 30	500 – 1,249	4
Blanco, 2012 [11]	RCT	16	16	24 – 28	<1,000	5
Bulbul, 2012 [12]	RCT	22	22	<32	AGA	4
Scattolin, 2012 [13]	RCT	60	55	<32	<1,250	3
Can, 2012 [14]	RCT	25	25	27 – 33	AGA	5
Morgan, 2014 [15]	RCT	74	76	<29 weeks	<1,200	5

[1]RCT, randomized controlled trial; AGA, appropriate for gestational age

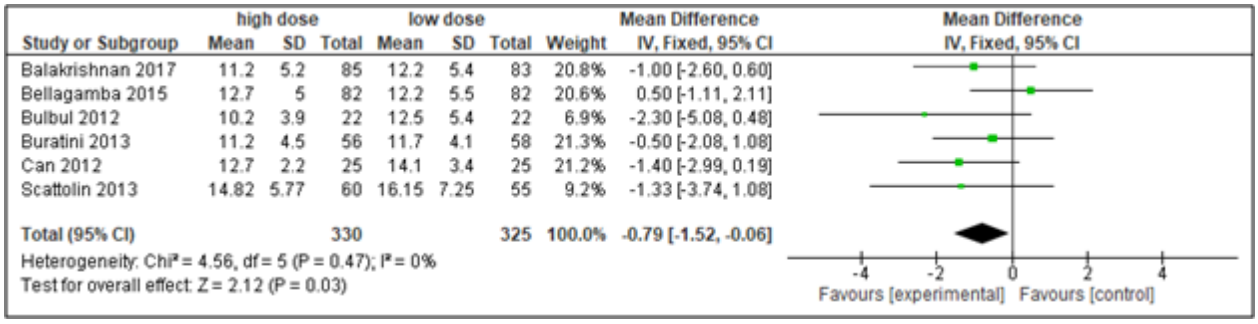

Figure 2. Forest plot for time to regain birth weight

Primary Outcome Measures

Reported measures throughout this section presented as mean differences with a 95% confidence interval.

Time to Regain Birth Weight

Six randomized controlled trial studies reported the time to regain the birth weight as one of their outcomes. There are six studies showed that administering early high-dose amino acids parenterally may reduce the time to regain birth weight in the preterm infants. Analysis of these studies showed a statistically significant reduction in the time to regain birth weight in the group of early high-dose amino acids administration in the preterm infants. Reductions were 0.79 day (MD 0.79 day, 95% CI 0.06 to 1.52 day; participants = 655; studies = 6; I2 = 0%) (P= 0.03) (**Fig. 2**).

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Body Length at 36 weeks

Three randomized controlled trial studies reported the length at 36 weeks (in Z score) as one of their outcomes. The result showed better growth of body length at 36 weeks on the early high parenteral amino acids dose, but not statistically significant with Z score difference at -0.11 (MD Z score 0.11, 95% CI -0.27 to 0.06; participants = 446; studies = 3; I2 = 43%; heterogeneity: low) (P= 0.20)(**Fig. 3**).

Head Circumference at 36 weeks

Three randomized controlled trial studies reported the head circumference at 36 weeks (in Z score) as one of their outcomes. The result showed better growth of head circumference at 36 weeks on the early high parenteral amino acids dose, but not statistically significant with Z score at -0.08 (MD Z score 0.08, 95% CI -0.23 to 0.08; participants = 446; studies = 3; I2 = 0%) (P= 0.32) (**Fig. 4**).

Length of Stay

Five randomized controlled trial studies reported the length of stay as one of their outcomes. Four out of 5 studies showed the beneficial effect of administering early high-dose amino acids in terms of length of stay. The studies showed a statistically significant reduction in the length of stay in the early high-dose parenteral amino acid groups. There is a reduction of 2.09 days of the length of stay in the infant who received early high parenteral amino acids compared to the low dose (MD 2.09 days, 95% CI 1.01 to 3.17 day; participants = 500; studies = 5; I2 = 0%) (P= 0.0002)(**Fig. 5**).

Secondary Outcome Measures

Sepsis: There are seven randomized controlled trials that measure the incidence of sepsis in both groups. There is no significant increase risk of sepsis in early low dose of parenteral amino acids administration (RR 0.80, 95% CI 0.61 to 1.05; participants = 796; studies = 7; I2 = 0%) (P= 0.11) (**Fig. 6**).

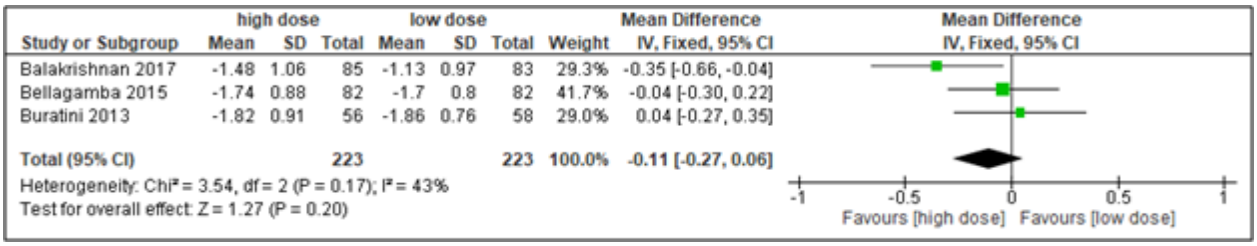

Figure 3. Forest plot for body length at 36 weeks

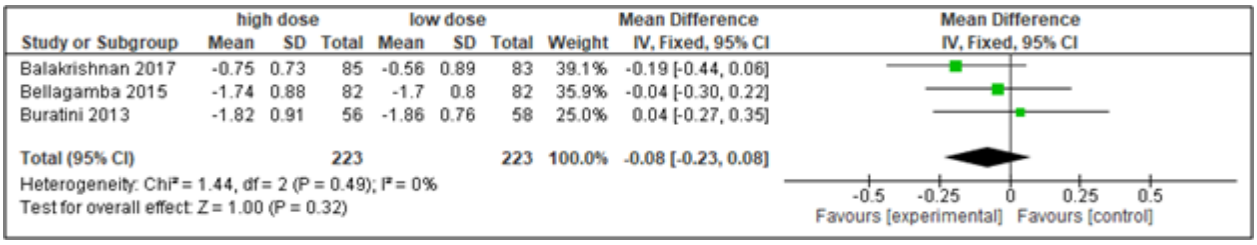

Figure 4. Forest plot for head circumference at 36 weeks

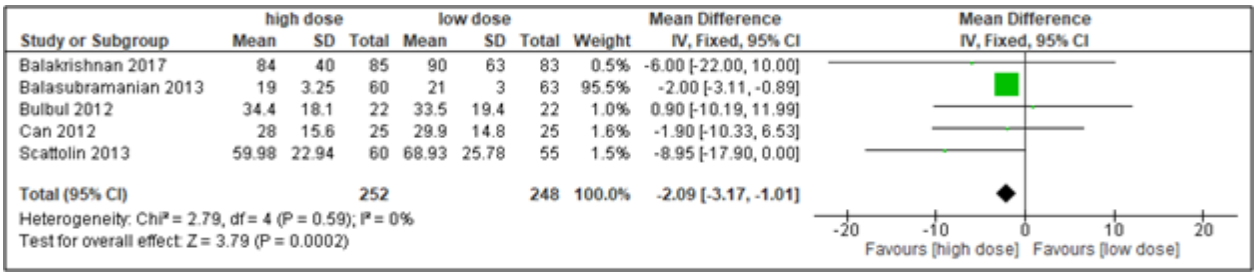

Figure 5. Forest plot for length of stay

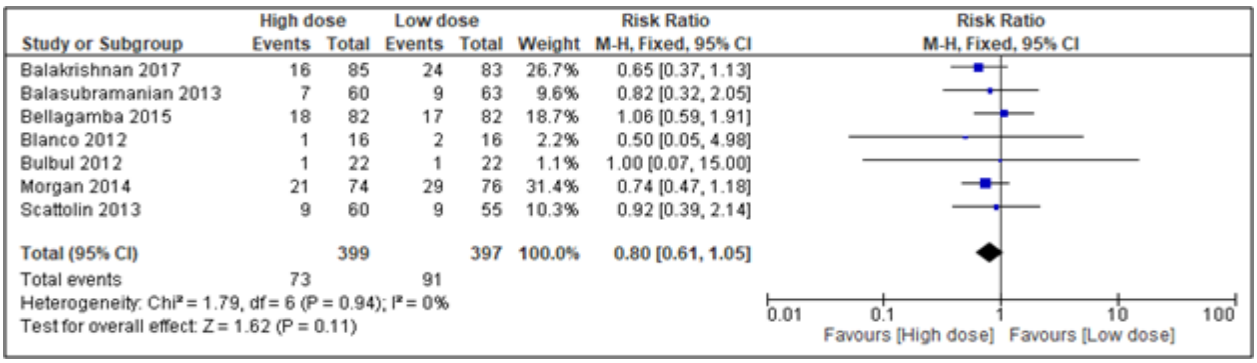

Figure 6. Forest plot for risk of sepsis

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Intraventricular Hemorrhage

There are seven randomized controlled trials that measure the incidence of intraventricular hemorrhage in both groups. There is no significant increase risk of intraventricular hemorrhage in early high dose of parenteral amino acids administration (RR 1.19, 95% CI 0.72 to 1.95; participants = 696; studies = 7; I2 = 0%) (P= 0.51) (**Fig. 7**)..

Patent Ductus Arteriosus

There are four randomized controlled trials that measure the incidence of patent ductus arteriosus in both groups. There is no significant increase risk of patent ductus arteriosus in early high dose of parenteral amino acids administration (RR 1.01, 95% CI 0.81 to 1.25; participants = 532; studies = 4; I2 = 0%) (P= 0.96) (**Fig. 8**).

Necrotizing Enterocolitis

There are eight randomized controlled trials that measure the incidence of necrotizing enterocolitis in both groups. There is no significant increase risk of necrotizing enterocolitis in early low dose of parenteral amino acids administration (RR 0.91, 95% CI 0.55 to 1.50; participants = 730; studies = 8; I2 = 0%) (P= 0.71) (**Fig. 9**).

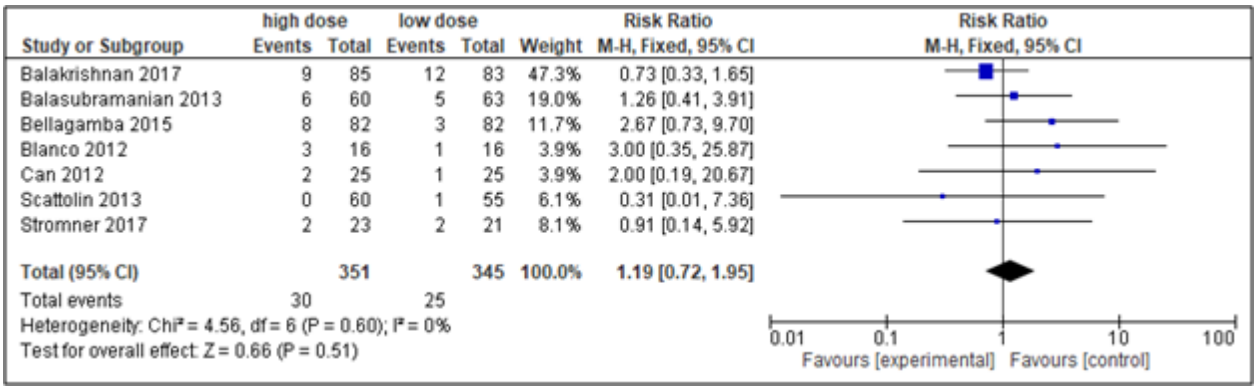

Figure 7. Forest plot for risk of intraventricular haemorrhage

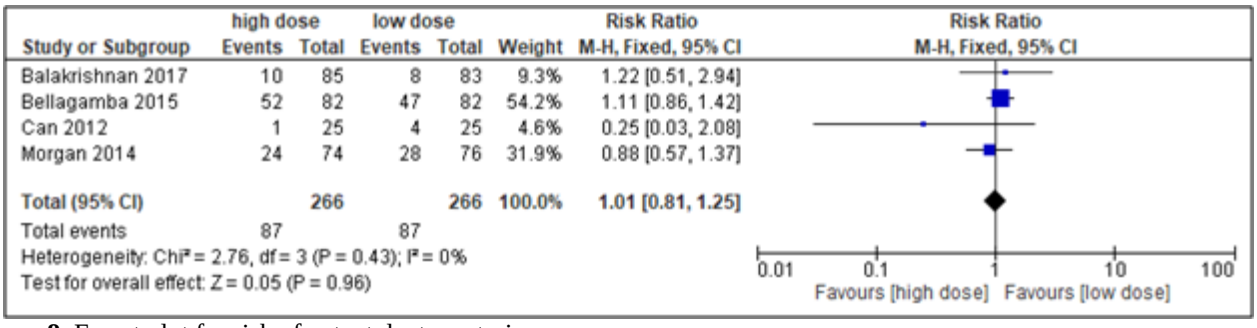

Figure 8. Forest plot for risk of patent ductus arteriosus

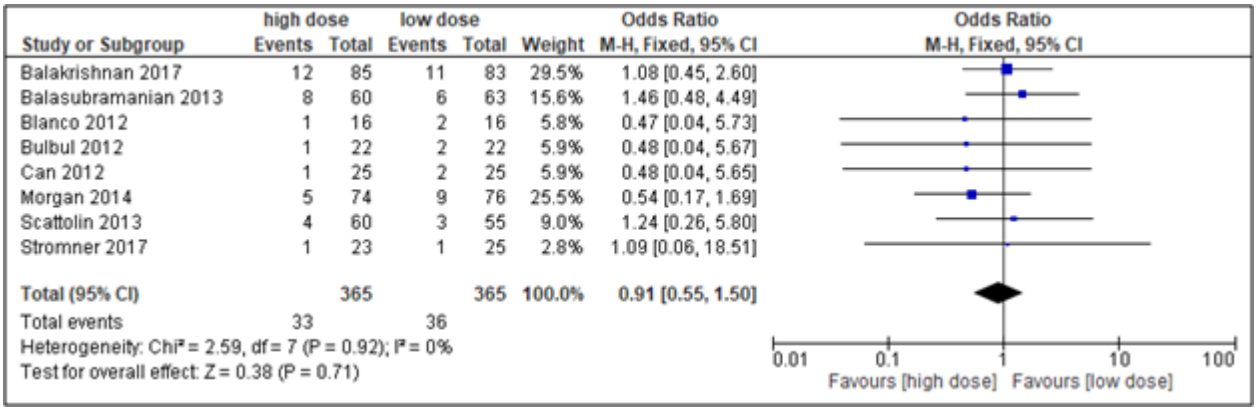

Figure 9. Forest plot for risk of necrotizing enterocolitis

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Retinopathy of Prematurity

There are six randomized controlled trials that measure the incidence of retinopathy of prematurity in both groups. There is no significant increase risk of retinopathy of prematurity in early high dose of parenteral amino acids administration (RR 1.08, 95% CI 0.76 to 1.55; participants = 752; studies = 6; I2 = 0%) (P= 0.67) (**Fig. 10**).

Bronchopulmonary Dysplasia

There are five randomized controlled trials that measure the incidence of bronchopulmonary dysplasia in both groups. There is a no significant increase risk of bronchopulmonary dysplasia in early low dose of parenteral amino acids administration (RR 0.93, 95% CI 0.75 to 1.14; participants = 641; studies = 5; I2 = 0%) (P= 0.48) (**Fig. 11**)

DISCUSSION

The result of our study found that early high-dose amino acids administration in the preterm infants has a statistically significant effect on the reduction of time to regain birth weight and length of hospital stay without any significant increase of morbidities such as sepsis, intraventricular haemorrhage, patent ductus arteriosus, necrotizing enterocolitis, retinopathy of prematurity, or bronchopulmonary dysplasia. There is no significant difference in terms of length and head circumference at 36 weeks of PMA.

The loss of the endogenous body protein is significant in preterm and even more significant in very preterm infants. This can be prevented by giving amino acid infusion as early as the first day of life. It can decrease protein catabolism, maintains insulin synthesis rates, and reduces the frequency of hyperglycemia in preterm infants.

Our result is consistent with the study conducted by Thureen et al., they found that giving higher amino acid (3g/kg/day) early in life, increased protein accretion by increasing protein synthesis and suppressing protein breakdown without showing any toxicity (16). Hence, we can conclude that administration of early high dose amino acids reduces the time to regain birth weight by preventing protein catabolism due to a negative protein balance in preterm infants.

The reduction of the length of hospital stay has a positive correlation with the time to regain birth weight in the preterm infants given an early and higher dose of amino acids parenterally. This significant result was also found in the study by Tang et al., which showed that intensive, higher dose (2.4g/kg/day), and early administration of amino acids improved preterm infants' growth, the tolerance of enteral feeding, and also reduces the length of hospital stays which overall reduced the cost of hospitalization (17).

There is no significant difference in the length and head circumference growth between two groups. This could be due to the variation of baseline length and head circumference between the two groups of the included studies. There is also no evidence that early high-dose amino acids cause increased morbidities like sepsis, intraventricular hemorrhage, patent ductus arteriosus, necrotizing enterocolitis, retinopathy of prematurity, or bronchopulmonary dysplasia. So, based on our study, we could safely initiate a high dose amino acids (target of ≥3g/kg/day) parenterally immediately after birth to our preterm infants, which may reduce the time needed to regain birthweight and lessen the length of hospital stay. Indirectly, it is reasonable to assume that this can help reduce the risk of hospital-acquired infections due to the prolonged stay at NICU.

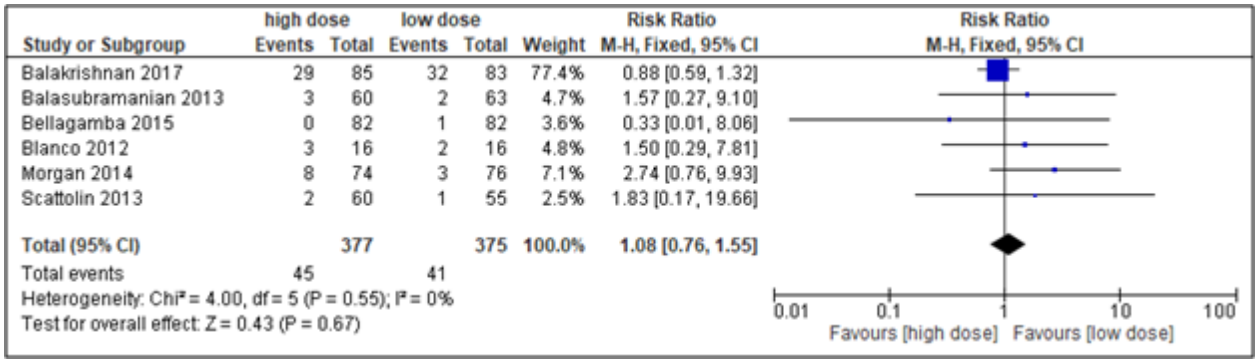

Figure 10. Forest plot for risk of retinopathy of prematurity

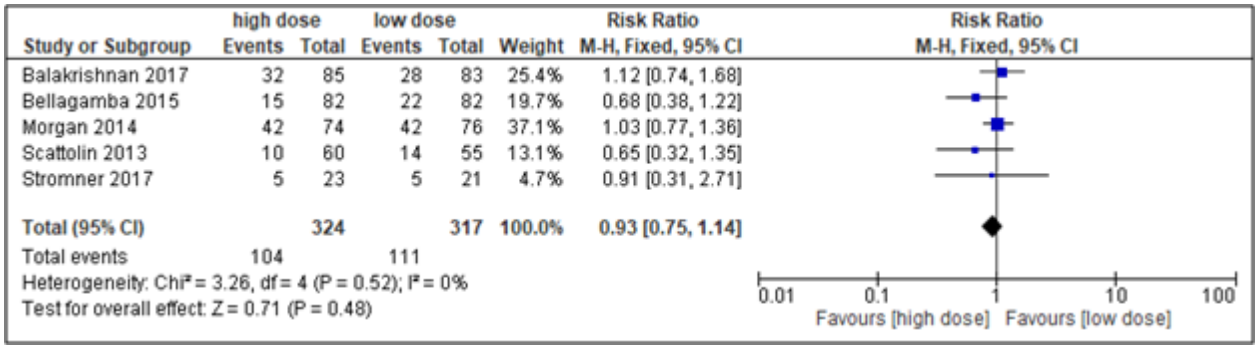

Figure 11. Forest plot for risk of bronchopulmonary dysplasia

CONCLUSION

In conclusion, this study results that the administration of early high-dose amino acids reducing the time to regain birth weight and the length of hospitalization in preterm infants. The analysis did not show any significant increase in the risk of morbidity. There is also noted insignificantly better outcome favorable to the high amino acids groups on the growth outcomes at 36 weeks PMA. From these findings, we could safely suggest and recommend administering a high dose amino acids in preterm infants within the first 24 hours of life. However, additional research efforts are still needed. We recommend that future trials hold more extended observation or longer follow-up timelines to assess the long-term effects of early high-dose amino acids administration and utilize Z-score for anthropometric outcomes to provide higher quality and more objective data. We hope this study can be the basis for future trials and guidelines in recommending early high-dose amino acids in preterm infants.

Author Contributions: TFD, MBRL; Study design, Literature review, Data collection, Statistical data analysis, TFD; Manuscript preparation, revisions

Acknowledgments: None

Conflict of interest: The authors declare no competing interests.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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