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THE EFFECT OF EARLY PARENTERAL NUTRITION ON RETURN TO BIRTH WEIGHT AND GAIN WEIGHT VELOCITY OF PREMATURE INFANTS WITH LOW BIRTH WEIGHT

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ABSTRACT

Early aggressive parenteral nutrition has shown its benefits in preventing extra-uterine growth restriction. However, in daily practice, clinicians still in doubts to implement it in newborns. This study aims to analyze the effect of early parenteral nutrition on gaining weight pattern. This analytical study uses randomized-unblinded-controlled trial design. The study carried out on 44 preterm infants with gestational age less than 33 6/7 weeks, birth weight between 1000-2500 grams and unable to receive daily nutritional needs through oral and enteral. A control group (n=23) received early parenteral nutrition since day 3 and a treatment group (n=21) received parenteral nutrition since day 1. Return to Birth Weight (RTBW) and Gaining Weight Velocity (GWV) are measured to represent gaining weight pattern. The results of this study, RTBW mean have no significant difference ($p \geq 0.05$) in both groups. The treatment group has a higher weight loss on day 1 and day 3 ($p<0.001$; p0.02) and did not have a weight loss difference on day 7, day 10, and day 14 (all $p \geq 0,05$). Both groups has faster GWV on day 1 and 3 but similar on day 14 (18 gram/kg/day and 16 gram/kg/day respectively). Early parenteral nutrition has no significant effect on RTBW and GWV.

1.Introduction

Preterm infants are likely to develop extrauterine growth restriction. The incidence of preterm birth in Indonesia is estimated to be more than 15%, while the incidence of low birth weight infants is at 9% per year (UNICEF, 2004; WHO, 2012). Earlier studies found that 68.4% of underweight infants who were born in Dr. Soetomo General Hospital have an abnormal General Movement and were at high risk for neurodevelopmental disorders in the future (Rochmah *et al.,* 2012). Extrauterine growth restriction increases the incidence of behavioural disorders, mental retardation and persistent learning impairment later in life (Moyses *et al.*, 2013). Consequently, early life nutrition is important. Inadequate nutrition intake, protein and energy deficits in the first few days of life, bacterial infections and organ system disorders due to prematurity are the risk factors of extrauterine growth restriction (Moyses *et al.*, 2013).

Once the umbilical cord clamped, maternal nutrition support is stopped immediately. Early parenteral nutrition seems mimicking previous nutrition support from the mother. Early parenteral nutrition effects on preterm infants have various results (Deidre and Diane, 2004; Hay, 2013; Kotiya and Zhu, 2015; Moyses *et al.*, 2013). American Academy of Pediatric Committee on Nutrition (AAP-CON) and the European Society for Paediatrics Gastroenterology, Hepatology, and Nutrition Committee on Nutrition (ESPGHAN-CON) suggest that early parenteral and enteral nutrition can prevent the incidence of extrauterine growth restriction in preterm infants and improve long-term outcomes, especially in neurocognitive function. Protein and energy deficits can be reduced, RTBW can be faster, and the incidence of necrotizing enterocolitis and late onset of sepsis will decrease. Anthropometric parameters showed improvement at 37 weeks of corrected age with a shorter duration of care in NICU (Neonatal Intensive Care Unit) (Deidre and Diane, 2004; Hay, 2013; Moyses *et al.*, 2013). Meta-analysis and systematic review studies suggest that early parenteral nutrition in preterm infants has no significant effect on mortality, NEC incidence, retinopathy of prematurity (ROP), intraventricular hemorrhage and cholestasis (Kotiya and Zhu, 2015; Moyses *et al.*, 2013).

Despite of existing evidences, it is still difficult to motivate and make sure all hospital staff members to implement early parenteral nutrition in daily practice. There is a need to conduct a study which analyses the effect of early parenteral nutrition on simple anthropometric-related parameters such as Return to Birth Weight (RTBW) and Gain Weight Velocity (GWV). RTBW and GWV are seen as parameters that reflect the short-term growth outcome. Therefore, this study aims to analyse the effect of early parenteral nutrition on RTBW and GWV.

2. Materials and methods

2.1. Materials

The design of this study is an interventional analytic study with a randomized unblended controlled trial design. This study was conducted in the intensive neonatology observation room at the Department of Pediatrics, Dr.Soetomo General Hospital, since August 2016. The subjects of the study were preterm infants born in NICU Dr. Soetomo General Hospital and in accordance with the inclusion criteria of the study. The ethical clearance of this research has been obtained from Dr. Soetomo General Hospital Ethical Commission Board. The parents signed the informed consent form before their children were included in the study. Information for consent was given before the parents sign the informed consent forms. A total of 44 infants were divided into two groups. The first group, the control group, consisted of 23 preterm infants who received parenteral nutrition since day 3. The second group, the intervention group, consisted of 21 premature infants who received parenteral nutrition since day 1. The inclusion criteria of the study are (1) preterm infants with gestational age of less than 33 6/7 weeks with the birth weight between 1000 and 1500 grams, (2) preterm infants with gestational age more than 33 6/7 weeks up to 36 6/7 weeks and birth weight more than 1500 up to 2500 gram that are not able to be given nutrition by oral or enteral (full enteral feeding) due to neonatal asphyxia and/or respiratory distress syndrome. The exclusion criterion is preterm infants who have multiple congenital anomaly and congenital heart disease and need fluid restriction. The weight of the new-borns were measured on daily basis. Then, GWV and RTBW were calculated from the daily weight measurement. GWV is the velocity of weight gain (gram/kg/ day) which is calculated by reducing the weight of the 14th day with the lowest body weight of preterm infant, then it is divided by the number of days since the preterm infant starts to gain weight. RTBW is defined as the time needed (in days) for preterm infants to regain weight at the same level as birth weight.

2.2. Statistical Analysis

The data were analyzed using Microsoft Excel 2016, Windows 10 and IBM SPSS Statistics 21. The data were presented descriptively for the basic characteristics of the two study groups. The Chi Square test and independent sample t-test were used to analyze homogeneity. The Chi Square test, Fisher test, Mann-Whitney U test and unpaired T-test were used to analyse the difference between GWV and RTBW from both groups. A 95% confidence interval and p value of <0.05 were used to determine the significance in this study.

3.Results and discussions

From 44 subjects who had met the inclusion criteria, 6 preterm infants were dropped out during the study period, 2 subjects from the treatment group and 4 subjects from the control group. The dropped-out subjects were all diagnosed septicemia. At the end of the study period, a final analysis of all the research subjects including the dropped-out subjects were performed. In this study, average gestational age when the baby were born was 31.52 weeks and the average birth weight was 1598.86 grams.

The average gestational age of the treatment group (31 weeks) is lower than the control group (33 weeks). The average birth weight of the treatment group was lower than that of control group ($p < 0.05$) (Table 1).

Table 1 Growth Patterns in Both Groups

Growth Patterns	Treatment Group (n=21)	Control Group (n=23)	p
TBW, median (min-max) (day)	8 (0-20)	7 (0-21)	0.85[1]
RTBW >14 days, n(%)	2 (9.50)	4 (17.40)	0.67[2]
GWV, median (min-max) (gram/kg/day)	18 (10-34.30)	16.33 (5-33)	0.14[1]
Post natal weight loss(%), median (min-max)	11.20 (0-20.20)	5.22 (0-23.66)	0.04[1]*

*Significant for $p < 0.05$, [1]Mann-Whitney U Test, [2]Fisher Test

Table 2. Parenteral Nutrition Composition in Both Groups

Parenteral Nutrition Composition	Treatment Group (n=21)	Control Group (n=23)	p
Carbohydrate (kcal/kg/day), mean (SD)			
a. Total	81.23 (±17.01)	69.18 (±13.70)	<0.001[2]*
b. Day-0	40.15 (±4.49)	33.64 (±6.86)	0.01[2]*
c. Day-3	72.34 (±9.77)	62.25 (±13.71)	<0.001[1]*
d. Day-7	88.93 (±16.06)	81.70 (±9.45)	0.09[2]
Protein (gram/kg/day), mean (SD)			
a. Total	3.25 (±0.25)	3.07 (±0.14)	0.02[1]*
b. Day-0	3	0	<0.001[1]*
c. Day-3	3.43 (±0.46)	3	<0.001[2]*
d. Day-7	3.25 (±0.58)	2.81 (±0.62)	0.06[2]
Lipid (gram/kg/day), mean (SD)			
a. Total	1.97 (±0.53)	1.55 (±0.13)	0.01[1]*
b. Day-0	1.5	0	<0.001[2]*
c. Day-3	2.13 (±0.64)	1.5	<0.001[2]*
d. Day-7	2.25 (±0.80)	1.70 (±0.27)	0.11[2]
GIR (mg/kg/minute), mean (SD)	7.06 (±1.70)	7.62 (±1.22)	0.21[2]

*Significant for $p < 0.05$, [1]Mann-Whitney U Test, [2]Independent T-Test

3.1. Mean Differences of RTBW and GWV between Treatment and Control Groups

Both groups did not differ significantly ($p \geq 0,05$) in the mean of RTBW, number of subjects with RTBW more than 14 days, and GWV. The statistical analysis of the postnatal weight loss parameter showed that the treatment group had a greater weight loss than the control group ($p = 0.04$) (Table 1).

The treatment group had a Δ weight loss of -1.26% from the birth weight at day 1, while the control group had a Δ weight loss of -0.55%. On day 3, Δ weight loss in the treatment group was -7.07% from the birth weight and in the control group was -3.29%. On day 7, Δ weight loss in the treatment group was-3.11% and in the control group was -0.12%. Using the statistical analysis, the treatment group had a larger Δ weight loss compared to the control group on day 1 and day 3 ($p = <0.001$; 0.02, respectively). The treatment groups did not have a Δ weight loss difference with control group on day 7, 10, and 14 (all $p > 0.05$).

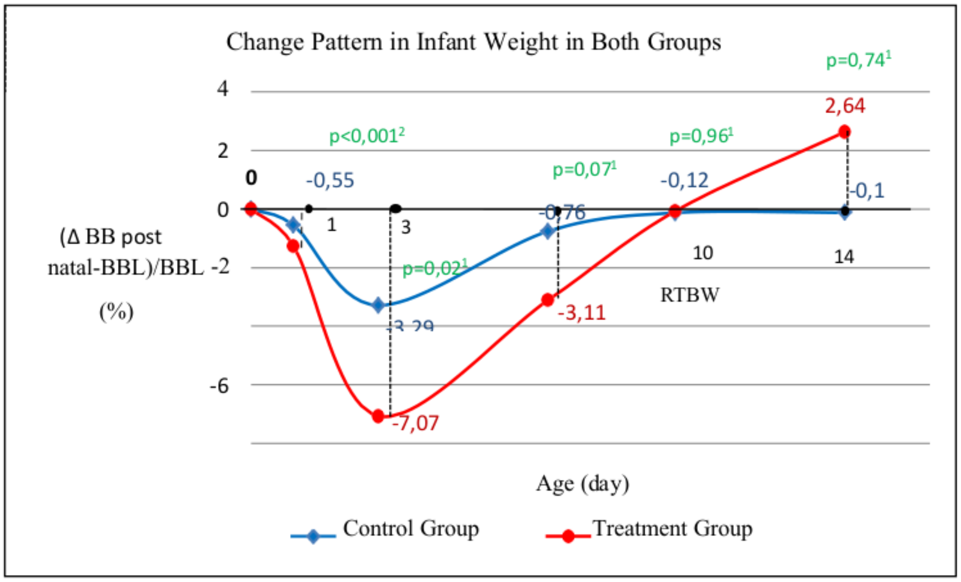

Figure 1. Change Pattern in Infant Weight in Both Groups

In this study, we analyzed the difference of parenteral nutrition mean composition between the two groups. The total and daily means of carbohydrates, proteins, lipids were counted since the subject received parenteral nutrition for the first time. The daily average of the parenteral nutrition components of both groups was calculated on day 0 (when parenteral nutrition was firstly initiated to the treatment group), day 3 (when parenteral nutrition was firstly initiated to the control group), and day 7 (mean of duration of parenteral nutrition given to both groups). The treatment group had a higher mean in total calories ($p <0.001$), calories on day-0 ($p = 0.01$), calories on day-3 ($p <0.001$), total protein ($p = 0.02$), protein on day-0 ($p <0.001$), protein on day-3 ($p <0.001$), total lipids ($p = 0.01$), lipids on day-0 ($p <0.001$) and lipids on day-3 ($p <0.001$). The mean calories on day-7, protein on day-7, lipids on day-7, and GIR did not differ between the two groups (Table 2). The treatment group had a lower median birth weight and lower first minute Apgar score, and faster GWV compared to the control group on observation day 1 ($p <0.001$), day 3 ($p = 0.02$), and had similar GWV on day 7, day 10, and day 14. Therefore, the RTBW between both groups did not differ at the end of the observation period (Figure 1).

3.2. Biochemical Monitoring of Treatment and Control Groups

On biochemical side effects monitoring, both groups had no difference in the random glucose test level, occurrences of hypoglycemia, serum triglyceride level, hypertriglyceridemia, direct bilirubin levels, total bilirubin levels, direct hyperbilirubinemia, mean BUN level, mean creatinine serum level, mean sodium level, mean potassium level, median chloride serum level and mean calcium serum level (all p ≥0.05) within the 24 hours of life. Both groups also had no difference in fluid balance and urine production on day 1, 3, and 7 (p ≥0,05)

3.3. Discussion

This study showed that aggressive parenteral nutrition did not seem to make difference in GWV and RTBW within the first week of life, although the treatment group had a higher weight loss than the control group. This could be explained because the mean birth weight was lower in the treatment group. Earlier studies showed that low birth weight infants are more at risk of extrauterine growth restriction than normal birth weight infants (Bolisetty *et al.,* 2014; Namiiro *et al.,* 2012). The treatment group in this study had one-minute Apgar score lower than the control group, but the five-minute Apgar score of both groups did not differ significantly.

The general characteristics of both groups in this study were same in terms of mean maternal age during delivery, mothers' perception towards pregnancy, history of premature pregnancy, and female sex's infant. The mother age during delivery which is more than 30 years [OR 0.41 (95% CI 0.20-0.82)], history of premature pregnancy [OR 2.4 (95% CI 1, 0-5,6)], female sex's infant [OR 1.23 (95% CI 0.84 to 1.81)], and unwanted pregnancy [OR 0.56 (95% CI 0.34-0, 93)] are the risk factors for intrauterine growth restriction in preterm infants (Viengsakhone, 2010; Zambonato, *et al.,* 2004). Preterm infants with intrauterine growth restriction had a double-risk for delayed GWV [OR 2.36 (95% CI 1.34-4.14)] and gain length velocity [OR 2.13 (95% CI 1.30-3, 50)] in the first month of life compared to low birth weight in term infants. In the third months of life, the risk of failure to grow increased [OR 5.89 (95% CI 3.07-11.30)] (Kiy *et al.,* 2015).

The daily measurement of infants' weight will not reflect gaining weight pattern because it only reflects the body water balance (Anchieta *et al.,*2004). Fenton and Kim (2013) recommend weekly weight measurement to observe the growth pattern of infants.

The effect of prenatal, perinatal, and post natal risk factors in the incidence of GWV and RTBW delay between both groups do not differ. Preeclampsia was not a risk factor for GWV delay [OR 0.47 (95% CI -0.10 s / d 1.05)] and height velocity gain delay [OR 0.2 (95% CI - 0.29 s / d 0.69)] in the first 3 months of life (Kiy *et al.,* 2015). In this study, the number of preeclamptic mothers in the treatment group was higher than that of the control group. An earlier study showed that the difference in proportion of mothers with pre-eclampsia in both groups might explain why the median infants' birth weight and mean Apgar score in the treatment group is lower than the control group (Chen *et al.,* 2014).

In this study, the treatment group showed a lower median birth weight and one-minute Apgar score, but their GWV was faster than the control group on day 1 and day 3, and had the same GWV with the control group on day 7, 10, and 14. Despite the faster rate of GWV in infants with early parenteral nutrition, GWV with or without early parenteral nutrition was still within the normal range of 14.8-20 grams/kg/day (Bertino *et al.,* 2008).

The treatment group received a higher daily intake of parenteral nutrition since day 0 because of the early initiation. On day 3, the control group has just started the parenteral nutrition intake, while the treatment group received a higher dose because of the increased titration dose. On day 7, the parenteral nutrition dose in both groups are the same. A higher dose of carbohydrate in the treatment group is followed by protein nutrition intake of 3gram/kg/day on the same initiation day, so that the mean GIR in both groups are the same.

The absence of abnormal laboratorial results of both groups showed that aggressive parenteral nutrition is considered safe to be implemented in infants (Liu *et al.,* 2015). Hypoglycemia was found to be asymptomatic in three infants in the treatment group and two infants in the control group. Infants have a higher risk of developing hypoglycemia within the first 24 hours after initiation of parenteral nutrition (Lee, 2015). There was no difference in incidence of hypertriglyceridemia in both groups. Elevated triglyceride levels are not a risk factor for cardiovascular disease or obesity in adulthood (Cosmi *et al.,* 2011; Skilton *et al.,* 2011).

3.4. Limitation of study

This study was limited on the evaluation of GWV and RTBW for the growth parameter. The results do not reflect low birth weight growth pattern comprehensively. This study also only observes a short period of post natal age, so it is less likely to represent overall gaining weight patterns. Further studies are needed to expand the birth weight categories and include more preterm infants.

4. Conclusions

Early initiation of parenteral nutrition in preterm infants with low birth weight had no effect in the duration of Return to Birth Weight and Gain Weight Velocity. However, the acceleration of Gain Weight Velocity observed in the first 3-days of life reflects body fluids balance instead of growth.

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