THE EFFECT OF TWO STRATEGIES OF PARENTERAL PROTEIN INTAKE ON SHORT TERM PROGNOSIS OF LOW-BIRTH-WEIGHT NEONATES

By

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Running title: Parenteral Protein on Low Birth Weight Neonates

ABSTRACT

Background: *Parenteral nutrition, with protein as the cornerstone, is of utmost priority for preterm infants since enteral nutrition is initially difficult, risking detrimental effect on their nitrogen balance, growth, gut maturity, and overall health. Its best method of delivery is still a mystery.*

Objective: *In this study, the effects of two alternative parenteral protein administration regimens on anthropometric measurements, hospital stay duration, duration of oxygen reliance, time to achieve goal enteral intake and necrotizing enterocolitis (NEC) incidence, and mortality are compared.*

Subjects and methods: *In this randomized control trial, 40 preterm newborns weighing less than 1600 grams were included. According to the initial dose and increment of parenteral protein, they were split randomly into 2 groups: group 1 (high protein) received 3 gm/kg/day on the first day of life and 4 gm/Kg/day on the second day of life, and group 2 (low protein) received 1 gm/kg/day beginning on the first day of life and increasing daily by 1 g/kg up to a maximum of 4 g/kg/day.*

Results: *Both groups resulted in comparable growth rates evidenced by their anthropometric measures, incidence of NEC, the duration of oxygen reliance, and the time it took for group 1 patients to meet their target enteral intake and to be discharged were slightly reduced. (P-value= 0.181 &0.455, respectively).*

Conclusion: *Both protein delivery routes produced equivalent effects, however high parenteral protein administration starting on day 1 may reduce hospital stays and aid in achieving full enteral intake sooner than low protein administration.*

Keywords: *Parenteral, Premature, Protein, Neonates, Growth.*

INTRODUCTION

Prematurity is the main culprit of infant mortality and the primary basis for the need of neonatal intensive care unit (NICU) **(Armanian et al., 2019)**. The corner stone of their management and the determinant of their outcome is nutrition, as they need higher nutritional requirements because of the rapid growth and lower nutritional stores compared to full terms **(Groh-Wargo and Merlino Barr, 2022)**. For a premature newborn's long-term health to be established, early nutrition and growth are essential **(Panza et al., 2022)**.

Although enteral feeding should begin on day one of life and increase till attaining the full intake as soon as feasible, this is highly challenging to accomplish due to poor feeding tolerance **(Hay et al., 2017)**. This is due to gastrointestinal immaturity which in turn delays the increment of enteral feeding and also due to higher incidence of necrotizing enterocolitis (NEC) **(Rich et al., 2017)**. This makes the parenteral nutrition a necessity for these infants **(Embleton et al., 2007)**.

Parenteral nutrition serves as a transition from enteral nutrition, which may not be tolerated for a few days after delivery in preterm infants and is occasionally the only source of sustenance for the rest of the child's life. In order to stimulate growth and prevent deficiencies, parenteral feeding regimens are designed to supply sufficient and balanced amounts of energy, macronutrients, and micronutrients. **(Groh-Wargo and Merlino Barr, 2022)**. Parenteral nutrition is built on protein, which is crucial element for growth and development. **(Young et al., 2022)**. The best method of parenteral supplementation for premature infants is yet unknown **(Embleton and McGuire, 2019)**.

AIM OF THE STUDY

Our study's objective was to assess and compare the short-term outcomes of two parenteral protein-intake techniques in preterm neonates in terms of anthropometric measurements and their impact on hospital stay duration, duration of oxygen reliance and duration to meet goal enteral intake. Along with avoiding co-morbidities and problems, such as necrotizing enterocolitis.

PATIENTS AND METHODS

Ethical considerations:

1. Prior to conducting the study, the ethical approval of Research ethical committee, Faculty of Medicine, Ain

Shams university was obtained (FMASU MS 368/2021).

2. A written informed consent was obtained from each infant's parents/legal guardian before enrollment in the study.
3. All patients data were kept confidential and parents/legal guardians had the right to keep them.
4. All patients' parents had the right to withdraw from the study at any time without affecting their course of treatment.
5. There are no conflicts of interest regarding the research or publication.
6. No funds were obtained to conduct this study.

Sample size:

The sample size calculation was done using the EPI Info 7 program for sample size calculation, setting the confidence level at 95% and margins of error at 10% and based on the work done by **(Balasubramanianet al., 2013)**, the sample size of 20 neonates/group was required to detect the difference between the 2 groups.

Inclusion criteria:

1. Preterm neonates below 37 weeks' gestation.
2. Preterms with birth weight equal to and less than (≤) 1600 grams.
3. Those admitted to our NICU starting day 1 of life.

Exclusion criteria:

1. Full-term neonates (37 weeks' gestation or more).
2. Preterm neonates whose birthweight was larger than 1600 grams.
3. Neonates with intracranial haemorrhage, inborn metabolic errors, significant congenital anomalies affecting growth.
4. Neonates admitted after the first 24 hours of life.
5. Those suffering any condition requiring surgical intervention.
6. Neonates with intrauterine growth retardation (IUGR), which is diagnosed if the neonate is born below the 10th percentile for their gestational age in terms of weight and/or length **(Ott ,1987)**.

Methods:

Between 2020 and 2021, this randomized control study was carried out in the NICU of the children's hospital at Ain Shams University. We included 40 preterm newborns weighing less than 1600 grams' birth weight. Randomization was carried out

utilizing a straightforward process that uses a computerized random sequence. Regarding the blinding, neither the senior resident who assigned the neonates to the intervention nor the nurse who prepared the TPN for the infants' care were involved in the trial.

All of the included newborns underwent:

- Complete history taking with specific tress on (gestational age, prenatal, and perinatal history).
- Full clinical examination (head to toe examinations involving all systems), as well as anthropometric measurements (weight, length, and occipitofrontal circumference), and were followed up till discharge.
- Laboratory investigations: according to Ain Shams University NICU protocol, in addition to weekly serum urea (using Synchron CX – 9 Delta autoanalyzer (Beckman Instrument Inc; Scientific Instrument Division, Fullerton, CA 92634, 3100, USA) and serum pre-albumin (using Human prealbumin (PA) ELISA kit: Shanghai crystal daybiotech co.,LTD).

The included neonates were randomly divided into 2 groups (according to the initial dose and increment of parenteral protein):

Group 1 (high protein) received 3 grams of protein followed by 4 grams per kilogram daily, on days 1 and 2 of life, Group 2 (low protein) received 1 gram per kilogram per day on day 1 of life, increasing by one gram per kilogram daily until a limit of 4 grams per kilogram per day.

Parenteral intake of all included neonates decreased as the volume of enteral intake increased. According to our NICU procedure, the other components of parenteral nourishment were administered to both groups in a same manner. Both groups will adhere to our NICU protocol for enteral feeding, which calls for trophic feeding (10 to 15 ml/kg/day) and increasing by 10-15 cc/kg/day until full enteral intake (150 ml/kg/day), which is calculated for each baby according to weight (Sweet et al., 2019). If maternal own milk was not available, formula feeding was given instead.

Follow up: Anthropometric measures like weight, length and head circumference were performed twice weekly.

Statistical Analysis:

Data were gathered, edited, coded, and entered into IBM SPSS

version 23 of the Statistical Package for Social Science. In contrast to median and inter-quartile range (IQR), which would be used if the quantitative data had a non-parametric distribution, the Chi-square test was used to compare qualitative variables that were reported as numbers and percentages. Parametric data were expressed as mean, standard deviations, and ranges. Qualitative variables were presented as number and percentages and were compared using Chi-square test. Using an independent t-test, two independent groups with quantitative data and parametric distribution were compared as opposed to Mann-Whitney test was used in data with non-parametric distribution.

With quantitative data and a parametric distribution, Repeated Measures ANOVA was used to compare more than two paired groups, while the Freidman test was used for non-parametric data. The allowable margin of error was set at 5%, while the confidence interval was set at 95%. Consequently, the p-value was deemed significant if < 0.05- otherwise it is non-specific.

RESULTS

The results of our study will be demonstrated in the following tables and figures.

Table (1): Comparison between the two studied groups regarding demographic data and characteristics of the patients

		Group 1	**Group 2**	**Test value**	**P-value**
		No. = 20	**No. = 20**		
Gender	Female	11 (55.0%)	12 (60.0%)	0.102*	0.749
	Male	9 (45.0%)	8 (40.0%)		
Gestational age (weeks)	Mean ± SD	31.25 ± 0.85	30.65 ± 1.18	1.842•	0.073
	Range	30 – 33	29 – 33		

Both groups were comparable regarding demographic data

Figure 1 (1-A,1-B and 1-C): Comparison of serial anthropometric measures between both groups throughout 4 weeks of admission:

a. Demonstrating the weight in kg,
b. Length in cm
c). Occipito-frontal circumference (OFC) in cm.

Figure (1-A)

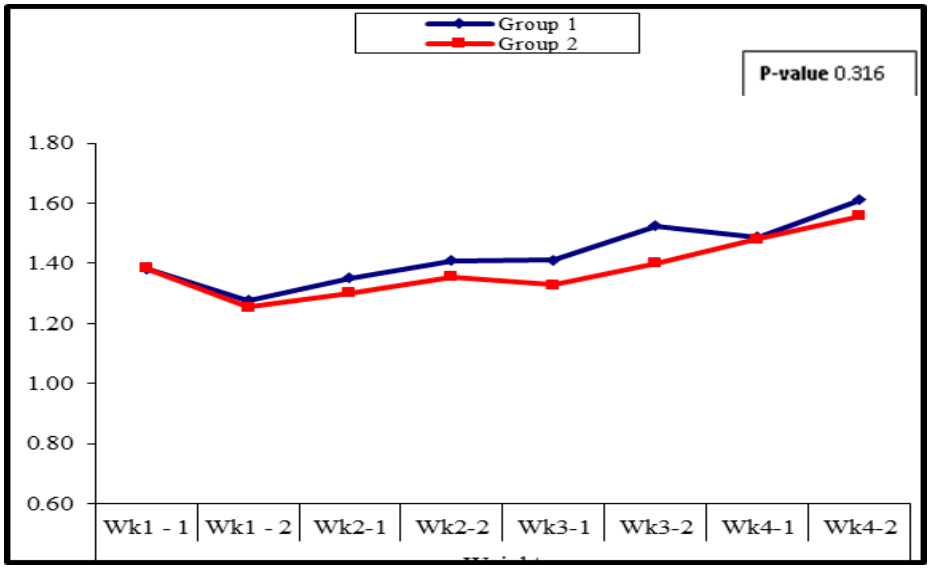


Figure 1-B

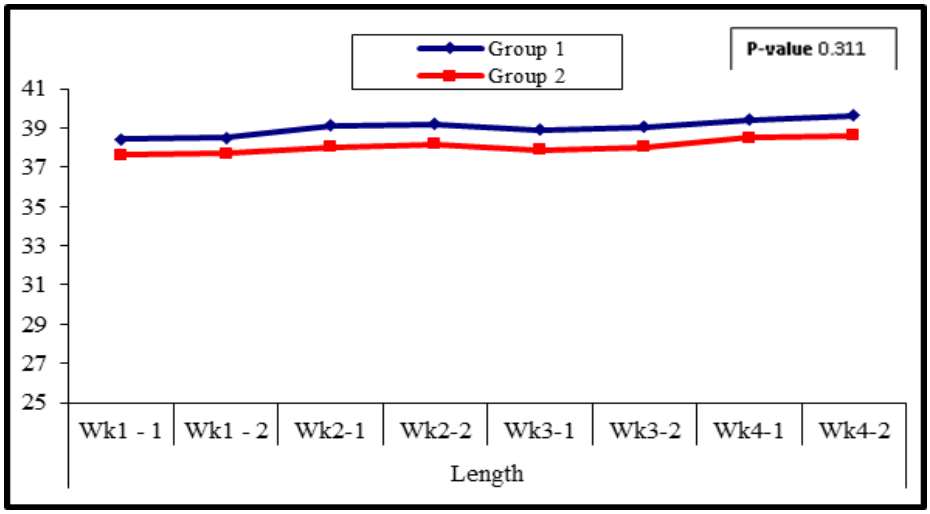
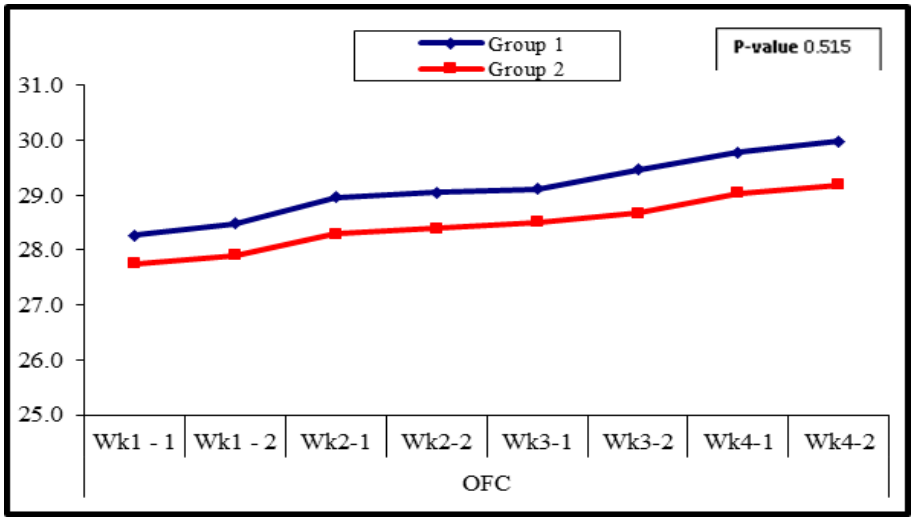


Figure 1-C



wk1-1: the 1st measurement in the 1st week, wk1-2 the 2nd measurement in the 1st week,
wk2-1: the 1st measurement in the 2nd week, wk2-2 the 2nd measurement in the 2nd week,
wk3-1: the 1st measurement in the 3rd week, wk3-2 the 2nd measurement in the 3rd week,
wk4-1: the 1st measurement in the 4th week, wk4-2 the 2nd measurement in the 4th week.

Table (2): Comparison of the difference of anthropometric measurements of the two study groups from admission until the end of the 4th week

		Group 1 (High protein)	Group 2 (low protein)	P-value
Difference in weight (kg)	Mean±SD	0.31 ± 0.14	0.27 ± 0.07	0.316
	Range	0.08 – 0.44	0.12 – 0.37	
Difference in length (cm)	Mean±SD	1.80 ± 1.29	1.28 ± 0.36	0.311
	Range	0.5 – 4.3	1 – 2	
Difference in OFC(cm)	Mean±SD	1.65 ± 0.84	1.86 ± 0.70	0.515
	Range	0.7 – 2.7	1 – 3.5	

Weight, length and OFC were done twice weekly recorded and plotted in figures (1-A,1-B and 1-C) and the difference between initial measurement on admission and at the end of 4th week were tabulated in table 2 where the 2 groups were found comparable **(Table 2)**.

Table (3): Comparison of serum pre-albumin levels (microgram/ml) between the two groups throughout admission

		Group 1	Group 2	P-value
End of 1st week	**Median IQR**	**435 (365 – 530)**	**320 (285 – 370)**	**0.003***
End of 2nd week	**Median IQR**	**750 (600 – 900)**	**550 (380 – 925)**	**0.100**
End of 3rd week	**Median IQR**	**975 (550 – 1400)**	**500 (320 – 550)**	**0.139**
End of 4th week	**Median IQR**	**980 (600-1450)**	**525 (350-870)**	**0.141**

Notes: values marked with asterisk (*) are statistically significant.

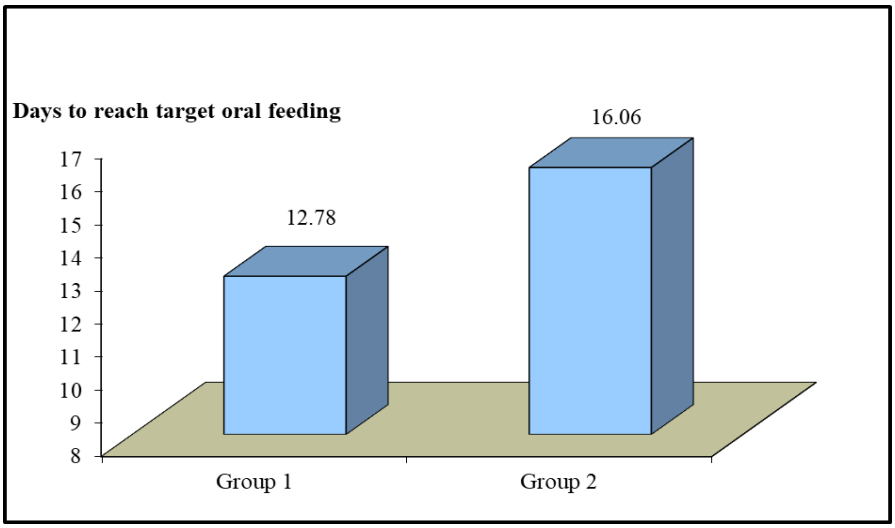
Regarding serum prealbumin, it was highly significant higher in high protein group during 1st week, and still higher in the same group in 2nd week and 3rd week but the difference wasn't significant **(Table 3)**.

Table (4): Comparison of serum urea levels (mg/dL) between the two groups throughout admission

		Group 1	Group 2	P-value
End of 1st week	Median IQR	22 (16 – 30)	17 (11 – 27.75)	0.177
End of 2nd week	Median IQR	21 (11 – 25)	13 (11 – 21)	0.482
End of 3rd week	Median IQR	21 (11 – 25)	13 (11 – 21)	0.482
End of 4th week	Median IQR	15.75 (15.5 – 38.5)	11 (9 – 13.5)	0.143

As for serum urea, the 2 groups were similar throughout the hospital admission **(Table 4)**.

Figure (2): Comparison of the number of days required to attain the target oral feeding for the two groups



Still the enteral feeding tolerance and time to reach the target enteral feeding were both better in the high protein group (P-value = 0.181) **(Figure 3)**.

Table (5): Comparison of the patients' outcomes and hospital stay between the two groups

		Group 1	Group 2	P-value
		No. = 20	No. = 20	
Duration of hospital stay (days)	Mean ± SD	21.85 ± 8.12	24.25 ± 11.66	0.455
	Range	8 – 45	10 – 45	
Days to regain birth weight	Mean ± SD	10.89 ± 3.05	11.35 ± 3.22	0.664
	Range	8 – 20	6 – 18	
Respiratory support	Negative	9 (45.0%)	7 (35.0%)	0.519
	Positive	11 (55.0%)	13 (65.0%)	
Days of respiratory support	Mean ± SD	12.73 ± 8.59	11.38 ± 5.72	0.652
	Range	3 – 30	1 – 20	
NEC (Necrotizing enterocolitis)	No	19 (95%)	19 (95%)	1.00
	Yes	1 (5%)	1 (5%)	
Mortality	Alive	17 (85.0%)	17 (85.0%)	1.000
	Died	3 (15.0%)	3 (15.0%)	

In terms of the duration to reach the birth weight or time spent with respiratory support or the hospital stay were all slightly shorter in the high protein group with no discernible difference from the other group. On the contrary, NEC incidence or mortality showed no difference between the groups **(Table 4)**.

DISCUSSION

The ultimate goal in management of preterm is to reach optimum weight gain, to mimic fetal growth rate, to reach target enteral intake in the shortest duration and to decrease length of hospital stay as much as possible. Optimizing parenteral nutrition will improve the prematurity outcome because it is crucial for the care of premature newborns **(De Curtis and Rigo, 2012)**. Protein is a keystone of TPN and it is an extremely important nutrient for growth and development **(Gothwal et al., 2016)**.

In developing countries, we have limited capacity of NICU places and limited resources, so improving the prematurity outcome while decreasing their length of NICU admission represent a crucial goal, not only for its impact on the parents and population but also for economic and medical importance as the NICU place is very precious due to the scarcity of places.

We sought to compare the short-term outcomes of two parenteral protein-intake strategies in preterm neonates in terms of anthropometric measurements, their impact on the length of hospital stay and the amount of time taken to reach the target enteral intake, as well as prevention of complications and co-morbidities.

Routine anthropometric measurements of the newborns are used to evaluate growth rate. The most prevalent indicator of growth is weight. Over the course of the first four weeks of life, both research groups gained weight similarly, but the high group gained a little more weight than the other group. Both groups' length and OFC increases were similar. In a similar trial, carried out by Lie et al. in 2020, one group was given parenteral proteins with a dose of 1.0-1.5 g/kg/day, which was increased by 0.5 g/kg, with the maximum dose being 3.5 g/kg/day and the other group, was started at 1.8–2.5 g/kg/day and increased by 1.0 g/kg, with a maximum dose of 4.0–4.5 g/kg/day, they found that the mean length and weight of the high protein intake group were greater than those of the low protein intake group, which was consistent with our findings, despite the fact that the differences between the two groups were not statistically significant **(Li et al., 2020)**.

In a similar trial conducted by **Naser et al. in 2021**, parenteral AAs were administered to the low protein group starting on day 2 at a dose of 1 g/kg/d and increasing

by 0.5 g/kg daily to a maximum of 2 g/kg/d. Neonatal length was shown to be statistically unaffected by the high group's parenteral AA administration, which started at a rate of 2 g/kg/d on the first day of life and increased by 0.5 g/kg every 24 hours to a maximum of 3.5 **(Naser et al., 2021)**.

On the VLBW population in India, Balasubramanian and his colleagues compared a group that started on day 1 by 3 gm/day and reached 4 gm/day on day 2 to another group that started on day 1 by 1 gm/day and found that the low protein resulted in better growth (weight, length, and head circumference) compared to early aggressive parenteral AA supplementation **(Balasubramanian et al., 2013)**.

We also found that the high protein group regained their weight slightly faster than the other group. Although, this difference wasn't statistically significant, it has a great indication and benefit. A newborn baby's growth, particularly that of a very low birth weight (VLBW) infant, is a reflection of how well its brain, liver, heart, muscles, and other body organs are developing **(Weaver, 2012)**. The goal is for the postnatal growth rate to be close to that of a healthy foetus **(De Curtis and Rigo, 2012)**.

While it's not unusual for healthy newborns to continue to weigh below birth weight beyond 14 days, it's usually acknowledged that they regain birth weight within that time frame **(Paul et al., 2016)**. With a mean of 10.89 days for the high protein group and 11.35 days for the low protein group, both of our groups achieved birthweight in the allotted time without any statistically significant differences. Unlike a study by Li and his colleagues, who noticed that there was a statistically significant difference in the time needed to regain birth weight between the groups receiving high protein intake and those receiving low protein intake **(Li et al., 2020)**.

Prealbumin is a liver-produced, unglycosylated plasma protein that exhibits variations in both protein synthesis and catabolism in response to starvation **(Myron et al., 2007)**. It is used to evaluate both the efficacy of nutritional therapy and the nutritional status of patients with protein deficiency. Prealbumin is a biomarker of growth in newborns that can be employed **(Kim et al., 2021)**. Pre-albumin levels in our study were considerably higher in the high protein group during the first

week, with a p-value of 0.003. It continued to remain higher in the following weeks without a statistical significance. We speculated that this difference was more prominent in the first week due to the higher total amount of protein intake in group 1 compared to group 2, but this difference wasn't found in the second week onwards as by then both groups reached the max protein supplementation. Despite employing varying amounts of AA supplementation, Naser et al. stated that AAs delivery in preterm newborns promotes albumin production, which can be shown as serum prealbumin **(Naser et al., 2021)**.

It is thought that serum urea is a sign of adequate protein consumption and amino acid oxidation. In the early days of life, urea concentration was found unstable in preterm newborns on TPN. **(Edelstein et al., 2021)**. It is used to compare protein turnover and is positively correlated with intravenous amino acid administration, but it still represents the burden on the kidney **(Giretti et al., 2021)**. Although serum urea in our study was slightly higher (without any statistical significance) in group 1 than in group 2, indicating that there was no greater burden on the kidneys as a result of this difference in AA administration strategy. Vlaardingerbroek et al found no appreciable variations in urea nitrogen levels between the two groups over the course of the hospitalization, indicating that high dosages of AAs do not raise the kidney load **(Vlaardingerbroek et al., 2014)**.

In our study, the high protein group had a non-statistically lower NICU stay. Still even one day less in the NICU implies a huge impact especially in low resource countries where NICU places are extremely precious. Even one day less can alleviate some of the financial and psychological burden on the community and government.

The high protein group was discharged 4 days' sooner than the other group as discovered by Lie et al. **(Li et al., 2020)**. Similar to this, Tang and his coworkers demonstrated that earlier and greater doses of amino acid delivery enhanced preterm infants' growth and tolerance of enteral feeding while also shortening hospital stays and lowering total hospitalization costs **(Tang et al., 2009)**.

Improving the gut maturity is a cornerstone in the improvement of the prematurity outcome. It is assessed by the tolerance of increasing enteral intake daily, so

it can be measured by the duration needed to achieve the full enteral intake. Higher protein supplementation is thought to enhance gut maturity as per **Tang et al in 2009** who stated that it also improved the growth rate and tolerance of enteral intake **(Tang et al., 2009)**. We detected a slightly shorter duration of reaching the target enteral intake compared to the other group which was 12.7±2.62, 16.06 ±9.8 days respectively in spite of having the same policy of enteral protein introduction and increment. This indicates better gut maturity which in turn decreases the parenteral nutrition dependence and thus improves the overall cost and expenses even if still admitted in NICU.

Additionally, we discovered that group 1 had much more enteral feeding on average during the first week, but this difference diminished over the course of the following weeks. According to Clark et al., preterm neonates who receive lower amounts of AA during their first week of life take longer than those who receive large amounts to obtain full enteral feeds **(Clark et al., 2007)**.

Regarding NEC, oxygen dependency, and death incidence, they were similar in both groups. In agreement with our findings, a prior study comparing the administration of low- and high-dose parenteral amino acids to extremely low birth weight infants found no differences in overall mortality, the length of oxygen supplementation and the incidence of NEC **(Leenders et al., 2018)**.

CONCLUSIONS

Both tactics had equivalent effects on growth, as evidenced by the weight and other anthropometric measurements, and they also helped to reduce the comorbidities in preterm neonates. Additionally, we found a modest advantage of higher protein intake in terms of shorter hospital stays and shorter time to attain enteral intake without endangering the kidneys. This has a major impact given our low resource environment and relatively restricted NICU capacity.

Recommendation

Higher parenteral protein gives the benefit of slightly shorter hospital admission and faster gut maturity with a comparable growth rate. Further research be done on this result using larger sample sizes.

LIMITATIONS

Relatively small number of patients which may be not enough to change the NICU protocols.

Author contributions:

Each author has met the authorship requirements. Hisham Abdel Samie Awad contributed to the conception and design of the study. He planned the study and revised the data and the manuscript. Mona Abd El Sabour Abd El Naeem contributed acquisition of data, analysis and interpretation of data. Basma Mohamed Shehata revised the data, and contributed to their analysis and interpretation. All authors were involved drafting the article or revising it critically for important intellectual content and final approval of the version to be published.

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