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EFFECT OF EARLY VERSUS LATE ENTERAL FEEDING IN PRETERM INFANTS ON THE INCIDENCE OF NECROTIZING ENTEROCOLITIS. A RANDOMIZED CLINICAL TRIAL

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ABSTRACT

Objective: The debate continues regarding the optimal timing for initiating enteral feeding and the rate of advancement in meal volume, due to concerns about predisposing young preterm to necrotizing enterocolitis (NEC). The aim of this study was to compare the effect of early versus late enteral feeding on the incidence of NEC. **Methods:** Overall, 60 preterm babies born between 28 and 34 weeks of gestation, admitted to the neonatal intensive care unit (NICU) between March 2023 and April 2024 were included. Based on whether enteral feeding was initiated within or after 48 hours since birth, the infants were divided into an early enteral feeding (EEF) group and a late enteral feeding (LEF) group. **Results:** Two cases (6.7%) of NEC were recorded in EEF group compared to one case (3.3%) in the LEF group. However, there was no significant difference in the incidence of NEC between the two groups (P = 0.5). In comparison with the LEF group, the EEF group was associated with a statistically significant decrease in the length of hospital stay, duration of total parenteral nutrition (TPN) use, and time to achieve full enteral nutrition (all P < 0.05). The daily weight gain was significantly higher in the EEF group compared to the LEF group (P = 0.0001). **Conclusions:** Early enteral feeding was associated with accelerated attainment of full nutrition, reduced duration of total parenteral nutrition and its potential complications, shortened hospital stay, without an increased risk of developing necrotizing enterocolitis.

KEYWORDS: Preterm, Enteral Feeding, Necrotizing Enterocolitis, Trophic Feeding.

INTRODUCTION

Necrotizing enterocolitis (NEC) is a disease characterized by inflammation and necrosis of the intestines, representing one of the most common gastrointestinal emergencies in newborns, particularly premature infants.[1] The incidence of NEC in preterm infants with a GA <32 weeks is reported to vary from 2 to 7.5 percent globally, across different neonatal intensive care units (NICUs).[2]

Due to concerns that enteral feeding may increase the risk of NEC, some high-risk infants have received prolonged periods of parenteral nutrition without enteral feeding. However, deficiency in enteral nutrients may impair the hormonal and structural functions of the digestive system by reducing hormonal activity, mucosal growth, lactase activity, nutrient absorption, or bowel maturation.[3]

Despite the association between NEC and enteral feeding, it remains uncertain whether feeding factors such as feeding advancement rate[4], timing of initiation[5], and trophic feeding[6] play significant roles in its occurrence.

Debate continues regarding the optimal timing for initiating enteral feeding and the rate of feeding advancement, primarily due to concerns about predisposing premature infants to NEC.[7] While earlier studies like E G Brown et al (1978)[8], and Carol et al (2003)[9] advocate delaying enteral feeding initiation, current data like Liang et al (2023)[10] support early initiation of trophic feeding and gradual feeding advancement in premature infants.

The practice of providing trophic feeding (small-volume feeding that provides the minimum calories) has been developed for some time postnatal as a strategy to enhance functional maturation of the gastrointestinal system. It was logical that if it was possible to improve feeding tolerance through minimal enteral nutrition (compared to the strategy of keeping infants "Nil per os" during the same period), this could potentially reduce the time to achieve full nutrition, the duration of parenteral nutrition use, and the length of hospital stay.

The aim of this study is to determine the effect of the timing of initiating enteral feeding on the occurrence of NEC.

MATERIALS AND METHODS

A randomized-clinical-trial was conducted at our neonatal intensive care unit (NICU), from March 2023 to April 2024.

The inclusion criteria encompassed all preterm infants admitted to the NICU at a gestational age of [28-34 [weeks. Exclusion criteria included preterm infants with signs of NEC, hemodynamic instability, perinatal asphyxia, cyanotic congenital heart defects, and congenital malformations of the gastrointestinal system.

The research sample included 60 neonates who met the inclusion criteria for the study after excluding 7 cases (3 cases due to hemodynamic instability requiring the use of vasopressor agent, and one case each for perinatal asphyxia, presence of NEC signs, death, and congenital malformation).

The research sample was divided into two equal groups based on the time at which enteral feeding was initiated, each consisting of 30 preterm neonates. The first group received early enteral feeding [EEF] within the first 48 hours of life, while the second group received late enteral feeding [LEF] after the first 48 hours of life.

The same enteral nutrition practice was followed in both study groups, where trophic feeding at a rate of less than 24 ml/kg/day was used for 7 days before starting to increase meal volume. Standard preterm formula was used due to the unavailability of human milk at all times.

Total parenteral nutrition (TPN) was initiated for all enrolled neonates from the first day of admission to the NICU at a rate of 0.5 grams/kg/day for both fat and protein, which was incrementally increased by 0.5 g/kg/day until reaching 3 g/kg/day. Once the milk volume reached 45 ml/kg/day, a gradual reduction of 0.5 g/kg/day was initiated until discontinuation.

After obtaining informed consent from the neonate's guardian, the following procedures were carried out: measuring length, weight, and head circumference at birth, determining gestational age based on the last menstrual period (LMP), and in its absence, relying on new Ballard score. A complete blood count, C-reactive protein (CRP), renal function tests with electrolytes (Na, K), and liver enzymes were performed for all patients within 24 hours of birth. Subsequently, abdominal girth and weight were monitored daily, signs of necrotizing enterocolitis were observed and classified according to modified Bell's staging criteria.[11] Additionally, the duration of TPN use, time to achieve full enteral feeding (FEF), and length of hospital stay were recorded.

Statistical analysis

The chi-square or Fisher exact test was used to study the relationships between categorical variables. The Independent T student test was employed to compare the mean differences between the two independent groups. All variables were tested using univariate regression, and the statistically significant variables were then entered into a multivariate analysis equation. The relative risk (RR) was measured, and confidence intervals were calculated. Results were considered significant if the p-value was less than 5%. IBM SPSS Statistics software was used to compute the statistical parameters and analyze the results.

RESULTS

Comparison of baseline characteristics

We collected a total of 60 consecutive preterm infants whom admitted to the NICU, during the period from March 2023 to April 2024. Seven cases were excluded and a total of 60 cases were finally enrolled fig. 1.

When the population was classified by the time of initiating enteral feeding, the EEF and LEF groups were equal (n=30 cases for both) fig. 1.

Table 1 shows the median times of hospital stay for the overall population, the EEF group, and the LEF group were 25.20±12.4 days (8-52 days) and 31.36±11.1 days (7-56 days), respectively (P: 0.04).

The frequency of NEC was higher in the EEF group, as there were two cases (IIA and IIB), with an incidence of 6.7%. In the LEF group, there was one case (IIA) with an incidence of 3.3%. However, there were no statistically significant differences with P-value: 0.5. Furthermore, the two groups did not significantly differ in terms of sex, gestational age, and birth weight (all $P > 0.05$) (Table 1).

Comparison of nutrition status

Table 2 shows the median grams of daily weight gain for the overall population, the EEF group, and the LEF group were 15.29±8.8 grams (- 13, + 40 grams) and 11.32±7.2 grams (- 11, + 38 grams), respectively (P: 0.0001). In addition, the duration of TPN use and the time needed to achieve full enteral feeding were significantly shorter in the EEF group than in the LEF group (all P: 0.0001).

DISCUSSION

There are diverse opinions on the optimal timing for initiating enteral feeding. Several studies have shown a correlation between early feeding initiation and an increased risk of developing NEC, while others have demonstrated a protective effect against NEC.

In our current study, which included two groups of preterm infants vulnerable to NEC, there was no statistically significant difference in the incidence rate of NEC between the two research groups. The present

finding was consisted with the results of Celic et al. (2009)[12] who showed that early enteral feeding did not increase the risk of NEC in very low birth weight infants. Although NEC occurred more in the late-feeding group than in the early-feeding group, which is opposite to our study, this may be explained by the fact that its average gestational age was lower than in our study and its larger sample size compared to ours. In addition, he reports some positive outcomes with EEF like increased daily weight gain. Our study is also consistent with this finding, as well as with a study by Liang et al. (2023).[13]

In the study by Akram et al. (2012)[14], early enteral feeding was associated with a shorter duration of TPN use (9.26±4.57 days in EEF versus 14.11±6.4 days in LEF with $P < 0.001$). This finding is consisting with our current study, and also confirmed in other studies like Liang et al. (2023).[13]

In the study by Liang et al. (2023)[13], there were a statistically significant difference in the duration of hospitalization and the time required to achieve full enteral feeding, as the duration was shorter in both cases in the early feeding group (43 days vs. 50 days) and (22 days vs. 29 days) with $P<0.001$ for both. This finding was consisted with our current study.

Flidel-Rimon et al (2004)[15], found that early enteral feeding was associated with a reduced risk of nosocomial sepsis in very low birth weight infants without change in the risk of NEC. In our study, we could not evaluate the role of EEF on nosocomial sepsis because most cases of sepsis in our NICU are diagnosed clinically due to the unavailability of blood cultures at all time and thus data analysis may be questionable.

While our study focused on NEC risk, other authors have reported serious complications like portal vein thrombosis and bleeding esophageal varices in infants who received umbilical catheterization for feeding purposes, underscoring the need for careful monitoring of feeding practices in this vulnerable population.[16]

Notably, NEC is one of the most common acquired gastrointestinal emergencies in preterm babies. Clinicians often delay the initiation of enteral feeding several days to avoid or reduce its occurrence. However, our study found that EEF did not increase the incidence of NEC, which consisted with the findings of Kwok et al.[17] Therefore, EEF could be safe in preterm infants and could be initiated early in life.

Limitations

The study duration was short, and the sample size was relatively small.

This is a single-center study, so the results may have limited generalizability to other NICUs with different feeding protocols.

CONCLUSIONS

Early trophic feeding within 48 h of birth, may have several benefits like improved nutritional tolerance, improved gastric emptying, decreased incidence of cholestasis, nosocomial infections, and decreased length of hospitalization, without an increased incidence of necrotizing enterocolitis.

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