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Early Enteral Feeding in Neonates Undergoing Esophageal Atresia Repair Surgery

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Abstract

Background: Neonates have limited reserves of energy. In esophageal atresia (EA) repair surgery, there were concerns about feeding initiation due to the location of the surgery.

Aim: To determine the effect of early enteral feeding on feeding tolerance and the duration of hospital stay in neonates with esophageal atresia.

Method: In this randomized clinical trial, 48 neonates who underwent type-C esophageal atresia surgery at Dr. Sheikh (a subspecialty centers in eastern Iran), July 2015 - November 2017 were randomly divided into the intervention and control groups. In the intervention group, 48 hours after surgery, feeding was initiated once the absence of anastomotic leakage was confirmed by a chest X-ray. The control group received routine feeding from the fifth day after surgery. Feeding tolerance and length of hospital stay (LOS) were compared. Data were analyzed in SPSS-16 using Fisher's exact and Independent sample T tests.

Results: The mean weight before intervention was 2550.1±523.4 grams in control and 2540.6±856.0 grams in intervention groups. Results revealed no significant differences between the intervention and control groups in the frequency of feeding volume tolerance (P=0.48). The mean duration of NGT feeding , time to achieve complete oral feeding and LOS were significantly lower in the intervention group (P<0.05).

Implications for Practice: In EA repair surgery early enteral feeding improved feeding tolerance and decreased LOS. So the approach to feeding after EA repair surgery is recommended to be reviewed, and considering patient's condition, can be started earlier even from 48^{th} hours after surgery.

Keywords: Enteral nutrition, Esophageal atresia, New born infant, Surgery

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Introduction

Esophageal Atresia (EA) is ultimately treated by surgery (1). Respiratory problems and feeding intolerance are the most common early post-surgery complications. Specifically, 13% of patients are hospitalized for more than 50 days (2). A hyper-metabolic response to surgery begins immediately after the procedure and leads to potential complications such as hypoglycemia, gluconeogenesis stimulation, protein catabolism and lipid oxidation (3). These complications are more serious in neonates, since neonates have smaller bodies, higher weight gain rate and immature body systems. Providing nutritional support to neonates undergoing surgery, including neonates undergoing atresia repair surgery, is therefore expected to profoundly affect their prognosis (4). Meanwhile, since gastric acid reflux to the esophagus is one of the most important causes of post-operative complications, in particular, anastomotic stricture, (5) even with a nasogastric tube, the oral intake of food is delayed until 5-7 days post-surgery (6). The reason is that the onset of nutrition increases acid secretion in the stomach. NGT also increases the chance of reflux (7) and contact with the stomach content at the site of surgery. On the other hand considering the positive effect of early enteral feeding and positive effects of breast milk on wound healing, some practitioners have initiated feeding 48 hours after atresia repair surgery; however, they have not provided any evidence in support of this practice (4, 5). Therefore, starting or not starting early enteral feeding in infants with esophageal atresia remained a clinical ambiguity.

In addition, another ambiguity in providing nutritional support to neonates with esophageal atresia is the enhanced volume during enteral nutrition. There are currently no specific guidelines on how to promote nutrition in these children. Nonetheless, the available literature recommends that nutrition must slowly be increased (5, 6) .Given that the onset of nutrition increases gastric acid secretion, even with NGT in the stomach, there is still a chance of reflux (8). Also, acid reflux increases the chance of stricture as a long term complication (5). Moreover, given that infants with atresia have a small stomach capacity due to the varying degrees of intrauterine misuse, gastro-esophageal reflux is very common once these infants reach full feeds (6). As a result, full enteral feeds can be reached in a timely manner. Given the lack of specific guidelines on this subject, this study proceeded with volume promotion according to premature neonates feeding volume increase (6).

Given the significant prevalence of the early and late complications of EA and the dramatic rise in the survival of neonates with EA, efforts should be focused on reducing complications and improving quality of life in these neonates (9). Therefore, considering the ambiguities about whether or not to start early feeding in infants with esophageal atresia this study aims to investigate the effect of early enteral nutrition on feeding tolerance and duration of hospital stay in neonates with EA.

Methods

This semi blinded clinical trial study (Statistical analyzer was blinded) is a part of a major sequential study on the early and long-term complications of EA neonates undergoing repair surgery and has been carried out at Mashhad University of Medical Sciences in Mashhad, Iran. The study population of this randomized, controlled, clinical trial consisted of the eligible neonates with type-C EA who had undergone surgery at Dr. Sheikh in Mashhad July 2015 - November 2017. The sample size was calculated as 18 based on the time to achieve complete oral feeding (Glass's delta Effect size = 2.188) (10) and using the formula of estimating sample size to detect mean differences in two independent communities and considering confidence interval of 95% and 80% test power. Considering approximately 20% sample loss, finally 48 neonates were included in the study, 25 neonates in the intervention group and 23 neonates in the control group.

Sampling was performed through the convenience method, and the selected neonates were divided into the intervention and control groups by block randomization, in blocks of 4 which was done manually (11). The inclusion criteria consisted of a distance between two pouches <3 cm, weight ≧1800 grams, physiological stability [HR=160-120, SPO ≧92%, RR=30-60, pink color, good tonicity] (12, 13) and gestational age ≥34 weeks, no concomitant abnormalities that affect nutritional status (including any major congenital abnormality). The exclusion criteria consisted of ventilator dependence, more than 48 hours of delay in weaning of the ventilator, anastomotic leakage, parents' or physician's withdrawal and the impossibility of initiating feeding for any reason.

The main variables included feeding tolerance (including feeding volume tolerance, duration of NGT feeding and time to achieve complete oral feeding, i.e. 100 cc/kg/day)(6) and the duration of hospital stay. Feeding volume tolerance means that the patient does not suffer from vomiting, regurgitation, stomach residual volume >50% of the feeding volume or abdominal distension and hemodynamic instability following NGT feeding or oral feeding. (13) The initiation of oral feeding comprised the baseline for calculating the duration of NGT feeding, and surgery day comprised the baseline for achieving complete oral feeding. After NGT removal, oral feeding continued as presented in Table 1.

In the intervention group, upon the confirmation of no anastomotic leakage by the CX-Ray 48 hours after surgery, NGT feeding was initiated with 2 cc/kg of breast milk every 2 hours and continued according to the feeding protocol as reported in Table 1 (6) .As can be seen in Table 1, feeding started at small volumes.

Based on the ward routine, the control group remained fasting for five days after the surgery and received parenteral feeding. In the absence of anastomotic leakage based on the CX-Ray on the fifth day, enteral feeding was performed for the controls similar to the intervention group (Table 1). A small volume was chosen for the control group for the following reasons: (1) Similarity to the intervention group because of the RCT nature of the research, (2) Probability of small stomach volume and proceeding with stomach volume increase, and (3) Preventing gastroesophageal reflux in the critical period of wound healing and taking into account the long-term complications.

After each feeding, the NG tube was occluded for 40 minutes and left open for free drainage until the next feeding. The patient was then monitored until next feeding (approximately 2 hours) in terms of feeding volume intolerance, including vomiting, regurgitation, increased residual stomach volume >50% of the feeding volume or abdominal distension and hemodynamic instability. If any of these conditions occurred, the patients were taken as cases of feeding volume intolerance, but feeding was not terminated and instead continued with the far smaller volume of 2 cc every 2 hours to maintain intestinal development and intestinal enzymatic function (6) .If the noted symptoms persisted or anastomotic leakage symptoms were observed, the neonate was no longer fed and was considered a case of research failure. To perform some additional analyzes, some laboratory parameters were extracted from the patient's file on the 5th day after surgery and entered in the relevant forms.

In terms of ethical consideration, early enteral feeding was performed under informed consent from the parents. Prior to obtaining parental consent, the potential benefits and risks of early nutrition were

Table 1. Feeding protocol for high-risk neonates (According to Fanaroff and Martin's Neonatal-Perinatal Medicine textbook (14))

Step	Volume every 2 hours	Total volume of the day
1	2ml/kg	24cc/kg
2	2 ml/kg q 2 hours * 6 If tolerated 3ml/kg q 2 hours * 6	36 ml/kg (Increase to 24 ml / kg / d)
3	4 ml/kg q 2 hours * 6 If tolerated q 2 hours * 6 5ml/kg	60 ml/kg (Increase to 24 ml / kg / d)
4	6ml/kg q 2 hours * 6 If tolerated 7ml/kg q 2 hours * 6	84 ml/kg (Increase to 24 ml / kg / d)
5	8ml/kg q 2 hours * 6 If tolerated 9ml/kg q 2 hours * 6	108 ml/kg (Increase to 24 ml / kg / d)
6	10ml/kg q 2 hours * 6 If tolerated 11ml/kg q 2 hours * 6	132 ml/kg (Increase to 24 ml / kg / d)
7	12ml/kg q 2 hours * 6 If tolerated 13ml/kg q 2 hours * 6	156 ml/kg (Increase to 24 ml / kg / d)

***ml/kg: Milliliters per Kilograms**

explained to them. They were ensured that their infant would be closely monitored throughout the intervention and would be promptly identified and managed in the event of any complications; and they were told that your child may be in the intervention or control group according to the randomization. The exclusion criteria accounted for risky cases, and such cases were immediately excluded from the intervention, but not from the study, and received specific care supervised by the PICU fellowship.
Data were analyzed in SPSS-16. The normal distribution of the quantitative variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Comparisons were performed using the independent-sample t-test and Fisher's exact test at the confidence level of 95% and significance level of 0.05.

Results
In this study 48 infants were included, 25 infants in the intervention group and 23 infants in the control group. One patient was excluded from the intervention group due to sepsis and apnea attacks and another one due to the non-cooperation of the physician. From the control group, one patient was excluded due to increased biliary secretion eight days after surgery and another because of severe respiratory distress and tachypnea. No other known complications, such as chylothorax, anastomotic leakage, anastomotic stricture, recurrent fistula or need for reoperation were observed (figure 1.).

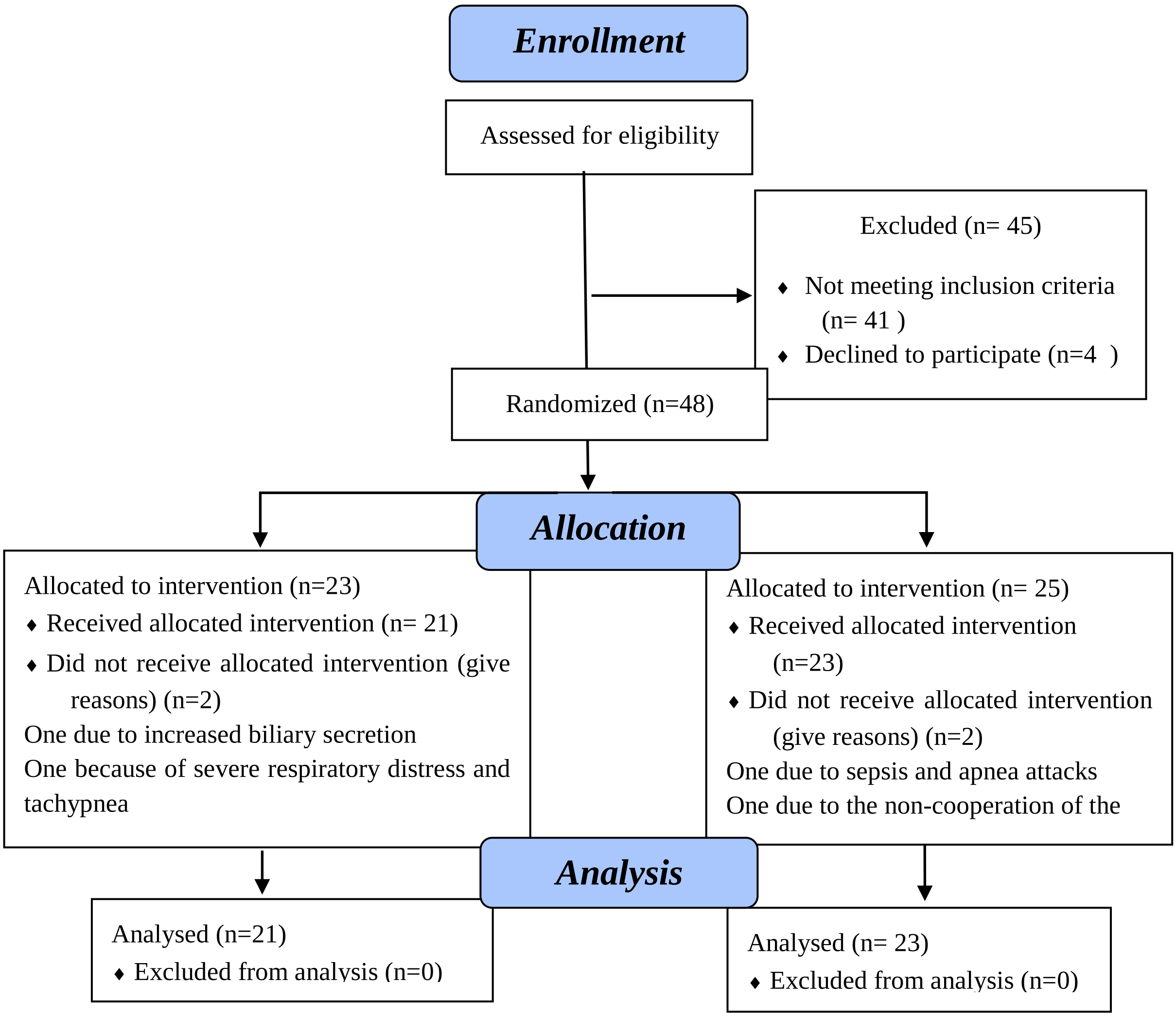

Figure 1. CONSORT Flow Diagram for study

Table 2. Duration of NGT feeding and time to achieve complete oral feeding (100cc/kg/day) and feeding tolerance after EA repair surgery in the intervention and control groups

Variable		Group		Effect size	P-value
		Control	Intervention		
		Mean ±SD 95% Confidence Interval	Mean ±SD 95% Confidence Interval		
Duration of feeding with NGT (day)		1.3±0.6 1.3 (95% CI 1.04 to 1.56)	0.9±0.7 0.9 (95% CI 0.614 to 1.19)	0.67	*P=0.01
Achieving complete oral feeding (day)		8.8±1.5 8.8 (95% CI 8.16 to 9.44)	6.7±0.9 6.7 (95% CI 6.33 to 7.07)	1.40	*P<0.001
Length of hospital stay (day)		10.8 ±1.5 10.8 (95% CI 10.2 to 11.4)	7.9 ±1.2 7.9 (95% CI 7.41 to 8.39)	1.93	*P=0.01
Feeding tolerance		Number (%)	Number (%)		**P=0.48
	Yes	18(85.7%)	21(91.3%)		
	No	3(14.3)	2(8.7%)		

*Independent sample T test
** Fisher exact test

The neonates' mean chronologic age at the time of entering the study was 2.4±1.2 days, their mean weight was 2.5±0.7 kg and mean gestational age 37.2±1.1 weeks. Final analysis showed that the mean chronological age in the control group (2.1 ±1.1 days) and in the Intervention group (2.7 ±1.4) (P=0.27); mean body weight in the control group (2540.6 ±856.0 grams) and in the Intervention group (2550.1 ±537.4 grams) (P=0.47) and mean Gestational age in the control group (37.3 ±1.0 weeks) and in the Intervention group (37.2 ±1.3) (P=0.56) according to Independent sample T test had No significant differences.
According to Fisher's exact test, the difference in the frequency of previous feeding volume tolerance between the intervention (91.3%) and control (85.7%) groups was not statistically significant (p=0.48).
The mean duration of NGT feeding was 0.9±0.7 days in the intervention group and 1.3±0.6 days in the control group, with a significant difference between them based on the independent t-test (p=0.01).
The independent t-test also showed a significant difference in the time to achieve complete oral feeding between the intervention (6.7±0.9 days) and control (8.8±1.5 days) groups (p<0.001).
The mean duration of hospital stay was significantly lower in the intervention group (7.9±1.2 days) compared to the control group (10.8±1.5 days) (p=0.01).
To facilitate the interpretation of the results, some laboratory findings are reported in Table 3.

Table 3. Laboratory findings of the neonates with esophageal atresia in the intervention and control groups at 5th day after surgery

Groups	Control	Intervention	Statistics
	Mean ±SD	Mean ±SD	
**CRP(mg/dl)	31.2±30.4	17.5±14.9	*P=0.03
Albumin (mg/dl)	3.3±0.3	3.6±0.2	*P<0.001
Total proteins (mg/dl)	5.1±0.4	5.4±0.5	*P=0.15
Total bilirubin (mg/dl)	7.8±3.9	6.0±3.4	*P=0.65
Direct bilirubin (mg/dl)	0.4±0.2	0.4±0.1	*P=0.65

*Independent sample T test, **C reactive protein,
mg/dl ;Milligram Per Deciliter

Discussion

The present findings suggest that early enteral feeding has no significant adverse effect on previous feeding volume tolerance, but reduces the duration of NGT feeding, the time to achieve complete oral feeding and the duration of hospital stay significantly. That is to say, feeding tolerance improved and the duration of hospital stay decreased in the intervention group.
The review of literature revealed no published articles on early enteral feeding after atresia repair

surgery, except for the data formerly published along the present data. Meanwhile, the comprehensive search carried out about early enteral feeding post neonatal surgery among articles published by May 2019 yielded eight related publications, which will be used for this discussion.

Schwalbe-Terilli et al. (2009) concluded that enteral feeding alone is often suboptimal after neonatal cardiac surgery. They proposed a need for new strategies to improve calorie intake to enhance postoperative recovery (15) .Further, Kalra et al. (2018) concluded that neonates tolerated feeds immediately following congenital heart repair and early feeding decreased the durations of mechanical ventilation and ICU stay (16) .

Ekingen et al. (2005) initiated enteral feeding 12 hours (eight to 20 hours) after surgery in the intervention group and after the return of bowel sounds in the control group. They found that early breastfeeding at a low volume is well-tolerated by neonates after abdominal surgery, even in cases of intestinal anastomosis (10).

Jiang et al. (2015) found that post-operative EEN using a jejunal feeding tube in upper digestive tract malformation in newborns is safe and easy and has fewer complications (17) .In a prospective cohort study, Raghavendra Prasad et al. **(**2018) concluded that EEN following abdominal surgery in neonates is feasible and well-tolerated and reduces the duration of hospital stay and mortality and the SSI score (18) .In a study conducted on gastroschisis repair surgery, Miranda da Silva Alves et al. (2016) found that the early start of enteral feeding and small gradual increase of volume can shorten the use of parenteral nutrition and ultimately reduce the incidence of infection and the duration of hospital stay in newborns with gastroschisis (19). Thompson et al. (2017) also found significant positive correlations between the time taken to initiate enteral feeding after abdominal closure and primary outcomes including the duration of NICU stay, duration of parenteral nutrition and time taken to regain birth weight (20). Meanwhile, Gulack et al. (2016) showed that the use of breast milk for the enteral feeding of infants following gastroschisis repair reduces the time from the initiation of feeds until discharge significantly (21). In our former RCT with a smaller sample size, we concluded that early enteral feeding in neonates with esophageal atresia repair surgery can improve the weight index in neonates with esophageal atresia (12).

Regardless of the study type and methodology, all the discussed studies supported early enteral feeding after neonatal surgery. An explanation may be that newborns have a smaller body, variable fluid requirements, rapid growth and maturation rate, increased caloric needs and low calorie reserves (6). Moreover, the hyper-metabolic response to surgery is conducive to potential complications such as hypoglycemia, gluconeogenesis stimulation, protein catabolism and lipid oxidation (3). All these factors can expose the newborn undergoing major surgery to more complications compared to adults. In addition, the prolongment of post-surgery starvation can lead to mucosal atrophy, villous flattening, increased intestinal permeability and decreased enzymatic activity. All these factors facilitate enteric bacterial translocation and further infections (10). On the other hand, delay in achieving full enteral feeding means continuing parenteral nutrition as much as possible, and this exposes the neonate to the side effects of parenteral nutrition including high risk of infection, need for central vein access and metabolic disorders(6).

These challenges are more significant in neonates with esophageal atresia. A neonate with esophageal atresia is fasting from before surgery, and because of the concerns about the effects of feeding on the anastomosis site, is kept NPO for a longer period of time, i.e. from five to seven days, based on neonatal textbooks (6). The patient receiving TPN also poses its own metabolic and technical complications, including increased free radicals and further suppression of the immune response (10).

One of the concerns about post-surgery feeding is regarding feeding intolerance that leads to delayed feeding initiation (22). Nonetheless, the present study showed that enteral feeding 48 hours after EA repair surgery does not enhance feeding intolerance, as also supported by the aforementioned studies. This finding could be due to the disappearance of the pathophysiological reactions of the neonate's body to surgery (23). Feeding type and method also highly affect feeding tolerance. Given that breastfeeding is consistent with the neonate's physiological needs and since breast milk is easily digested and absorbed, (6, 21) breastfeeding was taken as the main feeding substrate in this study.

In the present study, the duration of hospital stay was significantly shorter in the intervention group than in the control group, as supported by other studies (10, 16, 18, 20). Enteral feeding has various benefits, including enhanced immune system and reduced nosocomial infections and catabolic responses, all of which could shorten the duration of hospital stay. Given that breast milk contains immunity factors, early feeding with breast milk can improve the neonate's immune system (24). In this regard, Konnikova et al. (2015) used multiplex ELISA assays to quantify cytokines from fecal and serum samples at two weeks postnatal age and showed that delays in the enteral feeding of neonates is associated with intestinal inflammation and increased risk of morbidity (25).

Parameters associated with immune system function could be affected by the feeding status (26). Post-surgery infection causes an increase in serum CRP and pre-albumin levels (27). In the present study, the mean CRP was significantly higher in the control group compared to the intervention group. In general, CRP increases within a few hours of the onset of infection and inflammation, and it usually precedes pain, fever and other clinical indicators; it can therefore be assumed as a criterion for early infection detection (28). Higher CRP levels in the control group can indicate the higher tendency toward infection in this group, which could explain the longer hospital stay in the control group. Nevertheless, this explanation requires further clarification.

According to Table 3, the mean serum albumin level was significantly lower in the control group compared to the intervention group. While serum albumin level is taken as a protein synthesis index, increasing or decreasing serum albumin levels are adequate indicators of, respectively, the improvement or deterioration of the clinical state (29). Given neonates' liver immaturity, NPO before or after surgery adversely exposes them to the risk of reduced serum protein levels due to inflammatory mediators' synthesis. Initiating early feeding after surgery can thus prevent the reduction in serum albumin levels by offering the required substrate for various protein syntheses (30). In the present study, on the fifth day after surgery, serum albumin level was significantly higher in the intervention group, but not the total serum protein. Total serum protein mainly includes albumin and globulins (31). Significantly higher serum levels of albumin in the intervention group along with equal levels of total serum proteins between the two groups could be due to the different levels of serum immunoglobulins, which may ultimately be related to the immune status of neonates in the control group. This relationship could serve as a subject for further investigation.

Direct and indirect serum bilirubin levels were assessed to determine the possible effects of early feeding on cholestatic findings. Nevertheless, the higher but not significant quantitative values of direct and indirect bilirubin in the control group could be due to the increased enterohepatic cycling of bilirubin in fasting conditions (32).

The present study is the first conducted on early enteral feeding in esophageal atresia repair surgery. Despite the multiplicity of studies supporting early enteral feeding after neonatal surgery, none of them have been conducted on esophageal atresia patients. Moreover, some resources have proposed the advantages of early enteral feeding but have not offered any confirmatory baseline data. Meanwhile, in addition to the early complications, some late complications were also observed in this population, which may be adversely or positively affected by early enteral feeding, such as re-anastomosis and stricture. Nonetheless, there is still a lack of sufficient data to respond to these questions, and this study was established with more vigilance. Case mix comprises one of the strengths of this study, as the research was specifically focused on EA patients. This feature could increase the external validity of the findings.

The limitations of this research include the significant number of neonates with EA who also had congenital abnormalities, such as various cardiac or digestive problems; to achieve a homogeneous case mix, this population was not included in the study. Consequently, the results cannot be generalized to this population, which is recommended to be considered in a separate study.

This study is based on the Per-Protocol analysis approach and not the Intention to Treat approach, which could be a limitation, given the novel views about RCTs. In defense of their approach, the researchers would like to note the following: Sample leakage was not possible between the two study groups because the infants were not capable of non-adherence, which overlaps the results of the two types of analyses. Secondly, As for the cases that were eliminated due to complications, given that the number of eliminations in each group was only two, assuming any differences in the final results by incorporating these two neonates into the final analysis is unlikely. Finally, More importantly, the aim of a Per-Protocol (PP) analysis is to identify a treatment effect that can occur under optimal conditions (33), and this limitation could apply to any major protocol deviations in which the measurement of the primary endpoint is not available, which is also true about the present study.

Implications for Practice

The findings showed that early enteral feeding improved feeding tolerance and decreased the duration of hospital stay in the intervention group. The approach of feeding after EA repair surgery is recommended to be carefully reviewed, and considering patient's condition, early enteral feeding can be started earlier even from 48th hours after surgery. And it could be proposed that, in the issue of early enteral feeding, late complications should also be taken into consideration in the.

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Conflicts of Interest

There is not any conflict of interest. This study was supported by the funding provided by the Research Deputy of Mashhad University of Medical Sciences.

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