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Original Research

Time to achieve full enteral feeding in very low birth weight infants and Associated Factors in the Neonatology Unit

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Abstract

Introduction: Enteral intolerance in premature infants is associated with several morbidities, especially in very low birth weight (VLBW). There are only few dietary practices to provide better outcomes in newborns with VLBW. This study aimed to assess the factors associated with the time to achieve full enteral feeding (FEF) in infants with VLBW.

Methods: This was a retrospective study on infants with VLBW in the Neonatology Unit of Sanglah Central General Hospital, Bali from November 2020 to January 2022. The infants started trophic feeding with breastmilk and or formula milk. The age of FEF was determined when the target of 150 ml/kgBW/day was reached. The association of risk factors was analyzed using the Mann Whitney test, the Kruskal-Wallis test, and linear regression analysis.

Results: A total of 79 VLBW infants with the median gestational age of 30 weeks (25-38) were recruited. The median age of FEF was achieved in 9(7-15) days. Late trophic feeding (more than 24 hours), severe asphyxia, culture positive-sepsis, and using a mechanical ventilator were associated with a longer timing of FEF. While in the multivariate analysis, small for gestational age (SGA), late trophic feeding, severe asphyxia, absence of prenatal dexamethasone, and culture-positive sepsis were independent factors for longer FEF in this population.

Conclusion: In VLBW infants, the age of FEF in our population was reached in 2 weeks. Small for gestational age, late trophic feeding, severe asphyxia, prenatal dexamethasone coverage, and culture-positive sepsis were associated with delay in FEF. Further studies of multi-centers and analyzing the factors of delayed TF might be needed.

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INTRODUCTION

Feeding very low birth weight (VLBW) or very preterm infants poses a unique challenge due to the immaturity of the gastrointestinal tract. Early nutrition is crucial to improving optimal growth, long-term results, and reducing morbidities. The goal is to achieve a growth rate similar to that of fetal growth in utero. Malnutrition in the early stages of life has severe and irreversible consequences. Premature infants are more likely to have a risk of poor feeding intolerance, hemodynamically unstable, lack of breastmilk, which contributed to malnutrition and therefore a worse growth and development outcome [1]. Malnutrition in premature infants is associated with a smaller growth of the head circumference, poor neurodevelopment, motor function, and higher rates of cerebral palsy and autism [2].

Trophic feeding (TF) is defined as providing nutritionally insignificant volumes of enteral substrate to compromised infants to stimulate and supply nutrients to the developing gastrointestinal system. Trophic feeding supports gastrointestinal disaccharidase activity, blood flow, and microbial flora [3]. Clinical benefits include improved feeding tolerance, better weight gain, improved bone mineralization, reduced systemic sepsis, and shorter hospital stay; in addition, minimal enteral feeding facilitates a smooth and rapid transition from parenteral to enteral nutrition [3][4].

Almost all very low birthweight infants unable to tolerate substantial milk feeds should be considered for TF. Premature infants require enteral feeding assistance due to impaired swallowing and sucking abilities. Premature newborns have slower gastric emptying, sucking, and swallowing abilities than mature infants, especially at gestational age of less than 34 weeks [2]. These challenges are increasing especially in very low birth weight infants (VLBW; 1000 to 1500 grams). There are few dietary practices to provide a better outcome in VLBW infants. Nutrition should be started as soon as possible in premature and VLBW infants without morbidity. This practice will provide better endocrine adaptation, better immune function, and shorter hospital stays. In most cases, enteral feeding can be started in the first 3 days of life to achieve complete enteral feeding in two or three weeks [1].

Exclusions are infants with necrotizing enterocolitis or congenital gastrointestinal abnormalities, such as gastroschisis. As delaying feeding does not appear to confer any advantage, it is reasonable to start TF on day 1 or 2 of life, provided the infant is stable. It appears that 0.5-1 ml/kg/h is a safe and effective volume. The optimal duration of TF is difficult to recommend, and rather than specify a set time, regardless of clinical status, it is probably more sensible to suggest continuing TF until the infant can safely tolerate substantial volumes of milk. Breast milk, if available, should be preferred to formula [5].

Until recently, there was no study about enteral feeding and the duration of achieving full feeding in this population at Sanglah Hospital Bali. Taking into account the challenges and obstacles to providing adequate nutrition in infants with VLBW, our objective was to know the timing to reach FEF

in infants with VLBW in our unit and to assess the risk factors associated with it.

METHODS

This was a retrospective cohort study conducted between November 2020 and January 2022 at the Sanglah Central General Hospital Neonatology Unit, Denpasar, Bali. Ethics clearance was obtained from the Research and Development Unit, Faculty of Medicine with No. 1003/UN14.2.2.VII.14/LT/2022 Udayana University/Sanglah Central General Hospital. The sample size was calculated based on the formula of a single proportion corresponding to the study objective. The primary outcome was to determine the time to achieve full enteral feeding. The calculation of the sample size was determined with a total sample of 79. While for multivariate analysis, using the rule of thumb, 70 subjects were needed. All VLBW infants admitted to the Neonatology Unit of Sanglah Central General Hospital within 24 hours after birth were enrolled. Infants with major congenital anomalies, multiple congenital anomalies, anomalies of gastrointestinal anatomy that required surgery, or severe degree of hypoxic ischemic encephalopathy (HIE) were excluded. Data was collected from medical records. This includes demographic data, antenatal, neonatal and outcome data including sex, gestational age, birth weight, and risk factors. The results were analyzed with SPSS 21.0 software.

RESULTS

This study included 79 very low birth weight infants. Five infants, who died before reaching full enteral feeding (FEF) and one infant with a major congenital anomaly (gastroschisis), were excluded. Demographic data is shown in Table 1. The prevalence of males (45.6%) was slightly lower than females (54.4%). 14 infants were small for gestational age (SGA) (17.7%) and the rest were proper for gestational age (AGA). The median gestational age was 30 weeks (25-38), while the median birth weight was 1300 grams (1000-1500). Most infants were born with cesarean section (70.9%) and discharged from the hospital with a mean length of stay of 28.03 ± 18.17 days. The median age of trophic feeding (TF) was 33 (3-96) hours, while the median age of full feeding was 9 (7-15) days.

Factors Associated with Time to Achieve Full Enteral Feeding

The bivariate analysis (Table 2) showed the age of trophic feeding, severe asphyxia, culture-positive sepsis, and mechanical ventilator support as significant risk factors to delay full enteral feeding in this study, while the other factors were not significant. There was no significant relationship between the type of enteral nutrition (predominant breastmilk, predominant formula, or exclusive formula) and the time to achieve full enteral feeding, most of the infants had predominant formula (48 out of 79; 60.76%) as enteral nutrition, while neonates exclusively breastfed were none. 33 out of 79 (41.77%) infants got their first feeding (trophic feeding) in less than 24 hours, which they significantly associated with early time to achieve FEF.

Other factors, including SGA, delivery mode, prenatal dexamethasone, premature membrane rupture (PROM), fetal distress, hemodynamically significant PDA (Hs-PDA), hyaline membrane disease (HMD), necrotizing enterocolitis (NEC) and inotropic were not associated with the delay of FEF in our study.

Multivariate analysis

Variables with a P value <0.25 (age of TF, SGA, severe asphyxia, prenatal dexamethasone, culture positive-sepsis, mechanical ventilator, and NEC) were included in multivariate analysis using linear regression. Regression analysis (Table 3) showed that prenatal risk factors (SGA, prenatal dexamethasone), antenatal risk factors (severe asphyxia, delivery mode) and postnatal risk factors (culture-positive sepsis, hemodynamically significant PDA, age of trophic feeding) are all had a significant effect in the time to start full enteral feeding in our study with $p<0.05$ (Table 3).

From multivariate analysis, prenatal dexamethasone and the age of trophic feeding had a positive effect on starting full enteral feeding, while the remaining significant risk factors had a negative effect on the time to start full enteral feeding. The model has weak correlation with R^2 =32.0%, which means other unanalyzed factors might contribute to the duration of achieving FEF in this population.

Table 1

Neonatal Demographics

Demographics	Total (n=79)
Sex, n (%)	
Male	36 (45.6%)
Female	43 (54.4%)
Small/appropriate for gestational age, n (%)	
Small	14 (17.7%)
Appropriate	65 (82.3%)
Gestational age (weeks), median (range)	30.00 (25-38)
Birth weight (grams), median (range)	1300 (1000-1500)
Delivery mode, n (%)	
Spontaneous	23 (29.1%)
Cesarean section	56 (70.9%)
Length of stay, mean (SD)	28.03 (18.17)
Age of trophic feeding (hours)	33.00 (3-96)

Table 2

Risk factors for delayed full enteral feeding

Risk factors		n	Age of Full Feed (day)*		
			Median	Range	P-value
Type of enteral nutrition					
	Predominant breastmilk	25	9.00	2-12	0.45**
	Predominant formula	48	8.50	3-15	
	Exclusive formula	6	10.00	3-12	
Age of trophic feeding					
	>24 hours	46	10.00	3-14	0.03
	<=24 hours	33	8.00	2-15	
Small for gestational age (SGA) vs appropriate for gestational age (AGA)					
	SGA	14	9.50	5-12	0.23
	AGA	65	8.00	2-15	
Delivery mode					
	Caesarean Section	56	9.00	2-15	0.34
	Spontaneous	23	9.00	3-14	
Severe asphyxia					
	Yes	37	10.00	3-15	<0.01
	No	42	7.00	2-13	
Prenatal dexamethasone					
	Yes	56	8.50	2-15	0.06
	No	23	10.00	4-14	
Premature rupture of membrane					
	Yes	9	10.00	2-13	0.74
	No	70	9.00	3-15	
Fetal distress					
	Yes	7	10.00	3-15	0.29
	No	72	9.00	2-14	
Hemodynamically significant PDA					
	Yes	3	12.00	4-15	0.35
	No	76	9.00	2-14	
Culture positive-sepsis					
	Yes	11	10.00	5-14	0.01
	No	68	8.50	2-15	
Grade III-IV hyaline membrane disease					
	Yes	4	12.00	7-15	0.26
	No	75	9.00	2-14	
Mechanical ventilator					
	Yes	49	10.00	3-15	0.04
	No	30	7.50	2-13	
Necrotizing enterocolitis					
	Yes	15	10.00	2-12	0.07
	No	64	8.50	3-15	
Inotropic					
	Yes	4	10.00	4-10	0.80
	No	75	9.00	2-15	

*Full feed: 150 ml/kg/day; **analyzed by Kruskal Wallis

Table 3
Multivariate analysis

Multiple regression of time to full enteral feeding	β	Standard Error	Standardized Coefficients β	T	P-value
Small for gestational age	-1.749	0.808	-0.212	-2.165	0.034
Delayed age of trophic feeding	1.708	0.628	0.268	2.721	<0.01
Severe asphyxia	-1.905	0.649	-0.302	-2.933	<0.01
Prenatal dexamethasone	1.456	0.684	0.210	2.129	0.04
Culture positive-sepsis	-2.082	0.926	-0.229	-2.247	0.03

R^2 =32.0%

DISCUSSION

Early introduction and rapid achievement of full enteral feeding (FEF) is a priority in the nutritional management of preterm infants because it reduces the need for central venous catheters (CVCs), the risk of infection, and the length of hospital stay. On the contrary, delay in introducing progressive enteral feeding for VLBW infants has potential disadvantages, related to impairment of functional adaptation of the gastrointestinal (GI) tract. The need to quickly achieve FEF often conflicts with the physiological immaturity of GI function in preterm infants and the appearance of various comorbidities in the neonatal period [6].

The primary objective in full enteral feeding of VLBW is the achievement in the shortest possible time while maintaining appropriate development and nutrition and avoiding the negative consequences of the rapid advancement of feeding. Reaching this goal is more challenging than appears, and there are numerous disagreements [7]. In our study, the time to achieve full feeding was 9(7-15) days. Patwardhan et al. reported the same result, which the time to complete feeding achievement was 11(8-15) days [8].

Trophic feeding is defined as milk feeding of minimum quantities (10–15 mL/kgBW/day). It was first introduced to compensate for the lack of gastrointestinal stimulation seen during total parenteral nutrition. Gut priming, limited enteral nutrition, and early hypocaloric feeding are other terms for trophic feeding. Minimal enteral feeding activates gut hormones, improves structural and functional intestinal development, and reduces cholestatic jaundice and indirect hyperbilirubinemia. This practice promotes the action of gastrointestinal disaccharidase, blood flow, and microbial flora. The rapid transition from parenteral to enteral nutrition can also be achieved. Clinical advantages include increased feeding tolerance, better weight gain, enhanced bone mineralization, decreased systemic sepsis, and shorter hospital stay [1][9].

In our study, the median age to start trophic feeding was more than 24 hours [33 (3-96)]. In Dutta et al.[1] the ideal start for starting trophic feeding is as early as less than 24 hours of life. Enteral feeding can be started at 10-20 mL/kgBW/day and gradually increased by 20-30 mL/kgBW/day. In a study

conducted by Berti et al., [10] most VLBW infants started their enteral feeding in the first 24 hours of life (74%). While in the study conducted by Hendrayani et al., [11] most of the infants started enteral feeding in more than 24 hours (74.2%). Another study started trophic enteral feedings within 3 days of life or later, or at least a delay of 5 days [12] [13].

Small infants for gestational age were significantly associated with the time to full enteral feeding. Accordance to Bozzetti et al., [14], the significantly longer time for SGA infants compared to AGA to achieve complete enteral feeding ($p<0.0001$). After birth, babies with SGA are expected to have decreased intestinal function, which can lead to feeding intolerance. As a result, it took longer for SGA to reach full enteral feeding, which might be attributed to persistent prenatal intestinal hypoxic damage.

In this study, asphyxia was associated with a delayed time of full enteral feeding. The infant who is asphyxiated is at risk of bowel ischemia and necrotizing enterocolitis (NEC). Birth asphyxia can lead to gastrointestinal ischemia, which can result in injuries to the gut wall. Gastrointestinal damage can include injury to the bowel wall, which can be mucosal or full thickness and may even involve perforation. The amount of injury has an impact on nutritional management, particularly when it comes to initiating feeding in infants [15]. Zhu et al. reported that early initiation of enteral feeding in neonates with asphyxia is associated with gastrointestinal dysfunction such as vomiting and abdominal distension, and gastric bleeding. The percentage of gastrointestinal dysfunction on the first day was the highest in the first three days ($P < 0.05$) and not only dextrose but also dilute milk resulted in the dysfunctions. It is not optimal for newborns with asphyxia to early initial enteral feeding, especially in the first three days [16].

Prenatal dexamethasone was considered as one of the most effective methods to accelerate the time to reach full time feeding. A previous study supported our discovery of a positive effect on prenatal dexamethasone practice in VLBW infants. The effects of prenatal steroid intervention on gastrointestinal maturation include increased synthesis of intestinal enzymes and hormones, as well as improved intestinal motility. The growing intestine cells are particularly susceptible to steroids during the prenatal and shortly postnatal periods [14].

According to our study, sepsis has been recognized as a risk factor in postponed enteral full feeding in the study by Patwardhan et al.8 Inflammation and hypoperfusion play an important role in the pathophysiology of gut injury in sepsis. Sepsis increases apoptosis, decreases proliferation, and reduces epithelium migration. Furthermore, changes in tight junctions result in intestinal hyperpermeability and gut barrier dysfunction [18].

Human milk is the preferred feed for premature infants, as it offers in the short-term strong protection against infection and necrotizing enterocolitis (NEC) [13]. Enteral feeding, especially breastmilk, can reduce severity and incidence of sepsis itself [1][2][19]. Maternal breast milk or colostrum is the best initial enteral feeding for neonates. If this is not available, donor human milk is the

second option, while formula milk is the last option [1][9][20]. In our study, most of the infants were not exclusively fed breastmilk. There were 76% of the infants were predominantly fed by formula milk. Unfortunately, there was no human milk donor system in our unit, which might not be be the best practice and requires system improvement.

There was no significant association between HMD and time to achieve complete enteral feeding in our study. Our study was in accordance with the study conducted by Hendrayani et al. [11] that this association was not significant for the time it took to reach full enteral feeding (p=0.261). This finding was in contrast to Walsh et al. [21] Infants with HMD that cause respiratory distress syndrome are at increased risk of getting NEC due to delayed gastric emptying and disturbed intestinal motility.

In a study conducted by Fenin, Newman, and Taylor[7] in VLBW infants, the mechanical ventilator was not significantly associated with the time to achieve full enteral feeding. However, in our study, this is significantly associated. Some neonates with severe respiratory distress require mechanical ventilation support [15]. The mechanical ventilator has no direct effect on full enteral feeding. Gastric emptying is delayed in premature infants with acute respiratory distress during the first 72 hours of life and can delay the initiation of enteral feeding [22]. Based on the study by Kalra et al., [23] enteral feeding has been shown to reduce the time of mechanical ventilation. Neonates on trophic enteral feeding were extubated 30 hours earlier.

NEC is an inflammatory intestinal necrosis that affects preterm neonates once they begin receiving enteral nutrition. NEC affects 10% of preterm newborns weighing less than 1500 grams, or 1–5% of all hospitalizations in neonatal critical care units. It usually occurs between 7 and 14 days after delivery, while NEC has been observed many weeks later, especially in newborns with extremely low birth weight [24]. There are suggestions to delay enteral feeding and administer nutrition through the parenteral route due to feeding intolerance in NEC [25][26]. However, in our finding, it showed an insignificant relationship between NEC and time in achieving FEF.

Multivariate analysis showed that severe asphyxia was the strongest independent factor associated with full feeding achievement followed by culture positive-sepsis, prenatal dexamethasone, and small gestational age.

There was still a scarce number of publications on the time to achieve full enteral feeding in VLBW infants in Southeast Asia, especially Indonesia. This can be considered as the strength of this study to predict the incidence and risk factors in this population. The limitation of our study was that the observation was only done in a single center, leading to suggestion that variations between other centers might occur. Furthermore, this study did not analyze the cause of delayed TF which could be attributed to the longer time risk of achieving FEF.

IMPLICATION FOR NURSES

This study has nursing implications for the

description of factors associated with time to achieve complete enteral feeding. Nurses can determine what to associate for the time to achieve full enteral feeding in infants. So that nurses can provide intensive care and pay attention to these factors when caring for infants with very low birth weight. This research also serves as evidence for nurses who are starting to get full enteral feeding as soon as possible.

CONCLUSION

In summary, despite the challenges and complications encountered during the prenatal, antenatal, and postnatal periods, infants with VLBW should start receiving full enteral feeding as soon as possible. In this study, the age of FEF in the VLBW infants was reached in 2 weeks. SGA, late trophic feeding, severe asphyxia, prenatal dexamethasone coverage, and culture-positive sepsis were associated with delayed FEF.

LIMITATION

This research was conducted at Sanglah Central General Hospital. The results of this study can only be generalized in hospitals and the number of samples is limited due to the rare sample.

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COMPETING INTERESTS

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

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