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Original Research Article

Effect of early feeding regimen in pre-terms with abnormal antenatal dopplers: a prospective analytical cohort study

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ABSTRACT

Background: Enteral feeding in preterm neonates with intrauterine growth restriction (IUGR) and absent or reversed end diastolic flow (AREDF) on umbilical artery (UA) Doppler is delayed owing to an increased risk of necrotizing enterocolitis (NEC). Delaying enteral feeding with longer duration of parenteral nutrition (PN) carries an increased risk of various neonatal morbidities.
Methods: It was a prospective observational non randomized cohort study. Data was collected prospectively from the NICU records. Neonates fulfilling the inclusion criteria were classified as early feeding regimen and late feeding regimen. A strict feeding regimen was followed. Data was analyzed for primary and secondary outcomes.
Results: The 50 neonates were enrolled. Baseline characteristics were comparable. A significantly higher time to full feeds was recorded in the delayed feeding regimen by a mean of 3.9 days. The duration of hospital stay was significantly higher for delayed feeding regimen (+12.7 days). Days of mechanical ventilation were also significantly higher (+1.6 days) in the neonates in delayed feeding group. There was no difference in the incidence of feed intolerance, NEC, incidence of culture positive sepsis and mortality across the two regimens, however neonates in the delayed feeding group needed longer support with parenteral nutrition.
Conclusions: Early feeding will lead to earlier time to full feeds and decreased duration of hospital stay without additional increase the incidence of feeding intolerance and NEC in neonates with AEDF/REDF. Individualized feeding strategy in these compromised neonates should be the primary objective to optimize outcomes.

Keywords: Preterm, IUGR, AEDF/REDF, Feeding regimen

INTRODUCTION

Preterm infants are at increased risk of adverse neonatal outcomes.[1] At particular risk are those infants born after pregnancies in which Doppler studies of umbilical arterial wave forms reveal absent or reversed end diastolic flow velocities (AREDFV).[2] This phenomenon occurs in approximately 6% of high-risk pregnancies and is believed to result from increased placental vascular resistance in response to both acute and chronic hypoxia.[3] Lack of oxygen results in intrauterine growth restriction (IUGR) and the baby is often delivered preterm and small for gestational age.[4] Pregnancies complicated by suspected intrauterine growth restriction (IUGR) are usually monitored by Doppler ultrasound to measure fetal blood flow. A pattern of absent or reversed end diastolic flow velocity (AREDFV) in the umbilical artery is associated with fetal growth restriction and increased risk of intrauterine death. There is no consensus regarding how best to prevent NEC in small, preterm infants. Several strategies of poorly proven efficacy are in use including delaying feeds, slowly increasing feeds, use of

total parenteral nutrition (TPN) and prophylactic antibiotics.[5-7] In the present study and in the absence of recent studies from the region, we aim to establish the relationship between early vs delayed initiation of enteral feeds in preterm infants born with abnormal dopplers and the effect of two strategies on feed tolerance, time to full feeds and whether any of the strategies effect the incidence of NEC.

METHODS

The study was a single-center non-randomized trial conducted at a tertiary care NICU of Dayanand medical college and hospital, Ludhiana, India. Study period was January 2014 to December 2015. NICU practices included early aggressive PN through placement of UV catheters or peripherally inserted central catheters (PICC), weaning of PN once the enteral intake reached 120 ml/kg/day in extreme preterm and 110 ml/kg/day in very preterm, use of exclusive breast milk feeding with mothers' own milk or donor breast milk and complete avoidance of formula milk and routine use of human milk fortifier. Full feeds were defined as daily enteral feed volumes of 150-180 ml/kg/day for 3 successive days.

Inclusion criteria

Gestational age up to and including 36 weeks + 6 days (as per antenatal ultrasound or clinical or last menstrual period with antenatal ultrasound showing absent or reversed end diastolic flow velocities on Doppler waveforms from the umbilical artery on at least one occasion.

Exclusion criteria

Neonates with moderate to severe asphyxia (with base excess of more than minus 12 in blood gas analysis), Neonates with congenital anomalies.

Variables

Doppler sonography was used antenatally for non-invasive assessment of circulation in the umbilical artery. The estimate of gestational age was based on maternal last menstrual period, and when available, ultrasound-based assessment, and confirmed postnatally by new Ballard score. Small for gestational age (SGA) was defined as birth weight <10th centile for gestation as per Fenton's 2013 charts.[8] The number of deaths and morbidities were recorded in both epochs. Standard definitions were used for various morbidities during both periods and these remained unchanged. The severity of respiratory distress was graded by Silverman Anderson's retraction score.[9] BPD was defined as the need for supplemental oxygen at 36 weeks.[10] IVH was graded using Volpe's classification.[11] NEC was defined as per modified Bell's staging.[12] ROP was classified using the international classification of retinopathy of prematurity (ICROP).[13]

Grouping

Serially admitted preterm IUGR neonates <36 6/7 weeks eligible for the study were enrolled. Following initial stabilization by 12 h of age, babies were started on feeds as per the discretion of the attending neonatology team. Data recording was done to note the first time of feeding, time to achieve the full feeds, type of feeding, and factors affecting feed tolerance. After collecting the data, neonates were stratified in early feeding and delayed feeding groups.

Feeding protocol

Early feeding was defined as initiation of expressed breast milk (EBM) feeding within 12-24 h after birth, while late feeding was defined as initiation of feeds after 72 h after birth or later. Minimal enteral nutrition (MEN) with EBM was given in all cases and continued for 24 h. Feed progression using EBM was done at the rate of 10-15 ml/kg/day as per a feed advancement protocol (FAP) to achieve a stable, enterally tolerated volume of 150-180 ml/kg/day. Feeds were initiated if on assisted ventilation the FiO2 requirement was <0.4 or nasal continuous positive airway pressure (CPAP) <6 cm H_2O with a normal mean arterial pressure.

Outcome measures

The primary outcome measure was effect of the feeding regimen on time to establish full feeds. The secondary measures was whether the feeding regimen affects duration of hospital stay, difference in incidence of feed intolerance, incidence of NEC and effect on other co-morbidities related to prematurity.

Sample size estimation

Based on data collected at the institutional level and the standard practice of delaying starting of enteral feeds by 72 hours, mean time to achieve full enteral feeds was 10.2 days (±3.75). To consider significant reduction in time to full enteral feeds as 2.2 days (20% reduction), keeping two-sided significance as 95% and power of study as 80%, a total sample of 42 neonates (21 in each group) was needed to attain significance of results. An additional 20% was added to sample size to make total sample of 50 neonates (25 in each group).

Statistical analysis

The data were entered into Microsoft excel sheet version 1910, and analysis was done by using IBM SPSS version 24. Continuous variables were presented as mean ± standard deviation in normal distribution and median and interquartile range in skewed distribution. Categorical variables were expressed in frequency and percentages. Continuous variables were compared between survival and non-survival by performing independent t-test for normalised data and Mann-Whitney test for non-

normalised data. Categorical variables were compared by Chi-square test. For small numbers, Fisher's exact test was used wherever applicable. Multiple logistic regressions were performed to identify significant risk factors of mortality. Adjusted odds ratio and 95% confidence interval were calculated. P<0.05 was considered statistically significant.

Ethical clearance was obtained from the institutional ethics committee.

RESULTS

Eighty-eight neonates were eligible for inclusion out of which 38 were excluded due to various reasons (Figure 1). Fifty neonates were enrolled.

When we compared baseline characteristics across the two feeding groups, we did not find any statistically significant differences with respect to gestational age, birth weight, sex, LSCS deliveries, SGA status, need for resuscitation, coverage of antenatal steroids, incidence of PPROM and maternal PIH. (Table 1). Hence the two groups were comparable.

On analysis of various outcome measures across the two feeding groups, we found a significantly higher time to full feeds in delayed feeding group by mean of 3.9 days. There was no difference in incidence of feed intolerance and NEC across both the groups. The duration of hospital stay was significantly higher for neonates in the delayed feeding group (+12.7 days). Days of mechanical ventilation were also significantly higher (+1.6 days) in the neonates in delayed feeding group. Time to regain birth weight was significantly lesser for neonates in the early feeding group. There was no difference in incidence of culture positive sepsis and mortality across the two groups, however neonates in the delayed feeding group needed longer support with parenteral nutrition as compared to the early feeding group as shown in the Table 2.

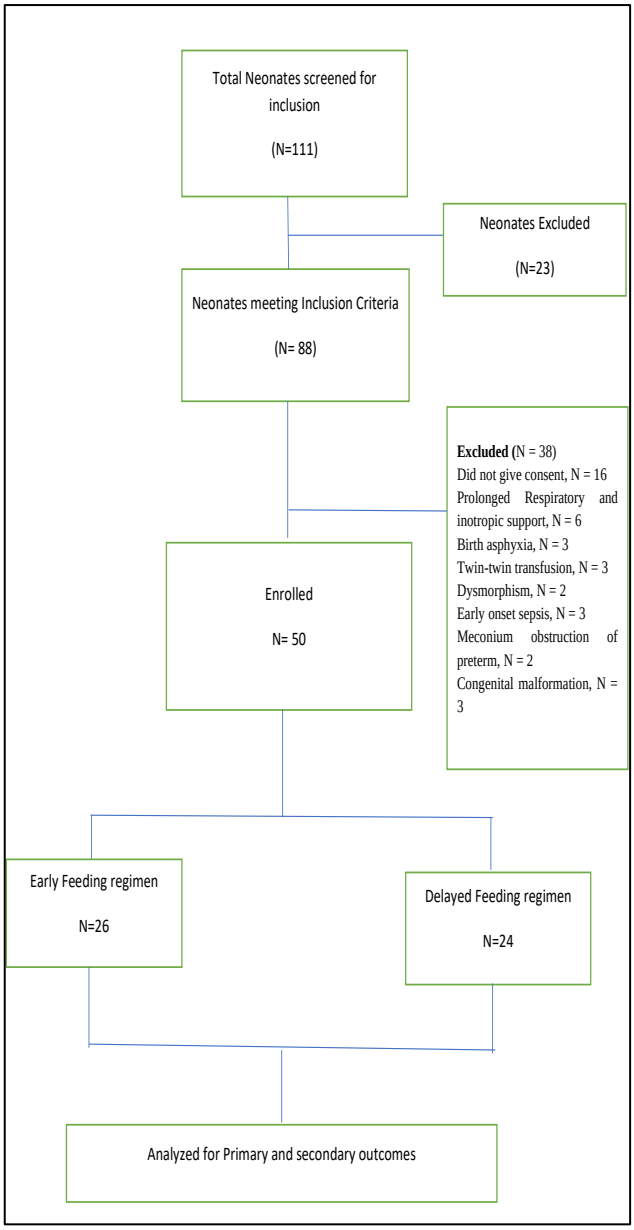

Figure 1: Study flow chart.

Table 1: Baseline characteristics.

Variables	Early feeding group	Delayed feeding group	P value
No of babies' n (%)	26 (50.9%)	24 (49.1%)	0.89
Gestational age weeks, mean (SD)	31.38 (±1.50)	30.99 (±1.88)	0.41
Mean birth weight, mean (SD)	1294.14 (±204.38)	1198.83 (±211)	0.11
Males	13 (50%)	16 (66%)	0.25
LSCS	20 (77%)	18 (75%)	0.87
SGA	15 (57.6%)	15 (62.5%)	0.72
Resuscitation as bag and mask and above (Yes)	4 (15.3%)	5 (20.8%)	0.61
Antenatal steroids	22 (84.6%)	19 (79.1%)	0.61
PPROM	6 (23%)	6 (25%)	0.86
Maternal PIH	17 (65.3%)	15 (62.5%)	0.83

Table 2: Outcome measures.

Variables	Early feeding group	Delayed feeding group	Mean difference (95% CI) or RR (95% CI)
Time to reach full feeds days, mean (SD)	8.0 (±2.35)	11.95 (±3.57)	MD 3.95 (2.24 to 5.65)
Incidence of feed intolerance, N (%)	8 (30.7 %)	8 (33.3%)	RR 0.92 (0.41 to 2.07)
NEC (Stage II and above)	1 (3.8%)	2 (8.3%)	RR 0.5 (0.04 to 5.18)
Duration of hospital stay days, mean (SD)	15.84 (±6.58)	28.6 (±8.25)	MD 12.7 (8.5 to 16.96)
Dutration of mechanical ventilation days, mean (SD)	3.2 (±1.5)	4.8 (±2.1)	MD 1.6 (0.56 to 2.63)
Time to reach birth weight days, mean (SD)	16.8 (±6.9)	24.2 (±11.3)	MD 7.4 (2.1 to 12.6)
Late onset culture positive sepsis, N (%)	2 (7.6%)	3 (12.5%)	RR 0.61 (0.11 to 3.37)
Mortality, N (%)	1 (3.8%)	2 (8.3%)	RR 0.46 (0.04 to 4.76)
Duration Of PN days, mean (SD)	6.3 (±2.8)	11.2 (±4.8)	MD 4.9 (2.68 to 7.11)

DISCUSSION

NEC remains an important comorbidity in neonates born preterm, which has various short and long-term implications.[14] In an effort to reduce NEC, NICUs across the world have tried delaying enteral feeds fearing NEC as the gut might be hypoxic especially in neonates with abnormal Dopplers which results in compromising nutrition in already compromised neonates.[15,16] Various studies have been conducted in the past to test if early initiation of enteral feeds is associated with earlier time to reach full feeds without increasing incidence of NEC.[4]

In the present study we documented that faster attainment of full enteral feeds in the early feeding group was not associated with increased incidence of feed intolerance and NEC. Moreover, when we delayed the onset of feeding in these neonates, we saw an increased duration of mechanical ventilation, an increased duration to attain the birth weight and an increased duration of PN days. Although we could not document an increased incidence of mortality and late onset sepsis as documented in various studies, we attribute this difference to insufficient power of our study to bring out significance of results for these outcomes. Our results prove that, the decision to delay enteral feeds in preterm neonates with abnormal dopplers should not be based on the convention that it will increase the chances of NEC as this will lead on to further complications already discussed adding onto cost of care. Following protocolized feeding regimen is more important factor which will result in reduction of NEC.

The results of the present study in preterm infants with IUGR and abnormal antenatal Doppler suggested that early introduction of MEF have insignificant effect on the incidence of NEC or feeding intolerance. This is in agreement with Van Ellburg et al who studied 42 infants, seeing only one case of NEC in the unfed group and with McClure and Newell who studied 100 infants, seeing one and two cases of NEC in trophic and control infants respectively.[17,18] The trial of Schanler et al contained 171 infants, with 13 cases of NEC in the trophic group, compared with 10 cases in the control infants.[19] Combining these results with those of the meta-analysis of Tyson and Kennedy, in 692 infants, NEC rates are similar at 10.5% for MEF and 9.4% for control infants (relative rate 1.07, 95% CI 0.84 to 1.36).[20] This also is in agreement with the results of the present study. A recent systematic review and meta-analysis on delayed introduction of progressive enteral feeds to prevent NEC in very low birthweight infants included three trials with 613 IUGR neonates with AREDF on UA Doppler. The effects estimate was 0.87 (95% CI 0.54–1.41) with no effect of delayed introduction of enteral feeds on NEC.[16]

Strengths of the present study include that there are very few studies from developing countries on this subject where earlier discontinuation of intravenous fluid use, earlier weaning from ventilator and earlier establishment of full feeds in the preterm neonate may result in shorter duration of hospitalization, avoidance of overcrowding in the NICU and lower incidence of LOS-related morbidity and mortality.

However, because of the relatively small sample size and randomized nature of this trial, large multicenter randomized controlled trials are required to further elucidate the role of feeding protocols and determine the factors that may play an important role in the pathogenesis of NEC and feeding intolerance in preterm infants with IUGR and abnormal fetal blood flow.

CONCLUSION

In conclusion, early introduction of enteral feeds in preterm growth restricted infants with abnormal antenatal Doppler results faster attainment of full enteral feeds and

has no significant effect on the incidence of NEC or feeding intolerance. Deciding individualized feeding strategy in these compromised neonates should be the primary objective to optimize outcomes.

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