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Comparison of Feeding Regimens in Preterm Neonates with Abnormal Antenatal Doppler: A Randomized Controlled Trial

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ABSTRACT

Preterm neonates with abnormal antenatal doppler results in the form of absent or reversed end diastolic flow or cerebral redistribution are at higher risk for the development of necrotizing enterocolitis due to impaired perfusion of the intestines in the initial few days. Hence the initiation of feeding is delayed, timing of starting feeds in these neonates according to protocols of various hospitals varies from first day to as long as one week, in order to reduce risk of NEC. Delay in initiation of feeds results in longer duration of parenteral nutrition and may increase incidence of sepsis related to intravenous access and perhaps increased duration of hospital stay. Early initiation of feeds is feared to increase incidence of NEC, but this risk should be balanced with the benefits of earlier time to full feeds and hospital discharge in case of early feeding. This trial was done to compare the safety and efficacy of early versus late initiation of enteral feeding in this special group of neonates.

Objectives: To evaluate the effects of an "early" enteral feeding regimen, starting milk feeds on day 2 after birth (between 24 and 48 hours of age) compared to one of "late" introduction of enteral feeds, starting feeds on day 6 after birth (between 120-143 hours of age) in a group of babies identified as being at high risk by antenatal Doppler studies.

Methods: This randomized, controlled, open, prospective, single-center clinical trial was conducted in a level III NICU in a tertiary hospital. 32 preterm infants (less than 37 weeks of gestation) were randomized to early feeding (n=16) and late feeding (n=16).After stabilization and admission to NICU and before initiation of enteral feeding before 24 hours they were randomized to early feeding or late feeding group. Time taken to attain full feeds, incidence of NEC and occurrence of complications were noted in the patients.

Results: Time taken to achieve full enteral feeds in the early feeding group was 13.86 (SD=5.41) as compared to 15.92(SD=4.08) in the late feeding group (p=0.031). 1(6.25%) baby in the early feeding group developed NEC as compared to none in the late feeding group which was not statistically significant. The duration of iv fluid was significantly less in early feeding vs late feeding group (11.73±4.36 vs 15±2.89,P=0.038). The incidence of other complications did not show any significant difference between the early and late feeding group.

Conclusion: Early initiation of feeding did not result in increased incidence of NEC as compared to late feeding. Incidence of other complications did not differ significantly between the two groups. Time taken to achieve full feeds and duration of iv fluid were significantly reduced as compared to the late feeding group.

KEYWORDS : Abnormal antenatal Doppler, early feeding, necrotizing enterocolitis,AREDF

BACKGROUND:

Preterm infants are at increased risk of adverse neonatal outcomes. 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) [1].This phenomenon occurs in approximately 6% of all high risk pregnancies [2] and is believed to result from increased placental vascular resistance in response to both acute and chronic hypoxia. Lack of oxygen results in intrauterine growth retardation (IUGR) and the baby is often delivered preterm and small for gestational age. The prognosis is poor compared to those with normal antenatal Doppler studies.[1-5] In infants with abnormal umbilical artery Doppler blood flow velocities it has been shown that blood flow to the head tends to be preserved to support growth of the brain at the expense of blood flow to the abdomen and growth of visceral organs[3,6,7]. In the earlier stages of fetal hypoxia (before AREDFV occurs) the changes of cerebral redistribution may be seen, with widening of the ratio of blood flow velocity in the cerebral artery to that in the umbilical artery - the cerebro-placental ratio. An increase in this ratio has also been associated with increased perinatal morbidity.[8-10].

Feeding babies born after AREDFV is a challenge: they are already under-nourished at birth, and good nutrition and growth is essential. However they frequently demonstrate intolerance of milk feeds and have been shown to have an increased incidence of necrotising enterocolitis (NEC).[1,3]

NEC is the commonest serious gastrointestinal emergency in neonatal intensive care units [11and is associated with a high mortality and morbidity] [12,13]. Extreme prematurity is the greatest risk factor, and whilst the specific aetiology is often not clear in individual babies, under perfusion and/or hypoxia of the gut are thought to be important predisposing factors [14,15].

Enteral feeding and bacterial invasion are commonly associated factors.[14,15] Reduced gut blood flow due to splanchnic vasoconstriction[1,3] may cause hypoxic-ischaemic damage to the intestine or its mucosa predisposing to NEC.

A recent meta-analysis [16] identified 14 observational studies comparing the incidence of NEC in infants who had exhibited fetal AREDFV with a group of controls. Nine of these studies show an excess of NEC in the AREDFV infants, with an overall odds ratio for developing NEC of 2.13 (95% CI 1.49-3.03) compared with controls with forward fetal umbilical end-diastolic flow.

The timing of introduction and rate of progression of milk feeds is an area of clinical uncertainty with arguments in favour of both early and late introduction of enteral feeds. Early introduction may improve nutrition and growth, but may increase the risk of NEC.[28] Conversely late introduction may be detrimental due to lack of stimulation of the gastrointestinal tract, resulting in villous atrophy and lack of hormone and enzyme production [28] and may not reduce the incidence of NEC. Prolonged use of parenteral nutrition increases the risks of sepsis, cholestatic jaundice and vitamin and mineral deficiencies. IUGR infants are at particularly high risk of parenteral nutrition-related liver disease.

There is no clinical consensus about how to feed growth restricted babies born prematurely after abnormal antenatal Dopplers. At the time of initiation of the trial there was paucity of data regarding the regimen of feeding in babies born to mothers with abnormal

antenatal Dopplers. This randomised controlled trial was aimed to determine whether a policy of early initiation of milk feeds is beneficial compared with late initiation. Outcome measures included, time to establish full enteral feeding, necrotising enterocolitis (NEC), sepsis and other complications. Optimising neonatal feeding for this group of babies may have long-term health implications and if either of these treatments is shown to be beneficial it can be immediately adopted into clinical practice.

Aim

To evaluate the effects of an "early" enteral feeding regimen, starting milk feeds on day 2 after birth (between 24 and 48 hours of age) compared to one of "late" introduction of enteral feeds, starting feeds on day 6 after birth (between 120-143 hours of age) in a group of babies identified as being at high risk by antenatal Doppler studies. The inclusion and exclusion criteria were as follows:

Inclusion Criteria:

- Gestational age up to and including 36 weeks + 6 days (dated by antenatal ultrasound or clinically).

- Antenatal ultrasound showing *either*

a) absent or reversed end diastolic flow velocities on at least 50% of the Doppler waveforms from the umbilical artery on at least one occasion during pregnancy *or*

b) cerebral redistribution, defined as occurring when both the umbilical artery pulsatility index is greater than the 95th centile and the middle cerebral artery pulsatility index is less that the 5th centile for gestational age.

- Postnatal age 0-24 hours

Exclusion Criteria:

- major congenital abnormality including known chromosomal abnormality
- twin-twin transfusion
- intra-uterine transfusion or exchange transfusion
- Rhesus iso-immunisation
- significant multi-organ failure prior to trial entry
- inotropic drug support prior to trial entry
- already received any enteral feeding

Methods:

Preterm infants (less than 37 weeks of gestation) with abnormal antenatal doppler suggestive of absent/reversed end diastolic flow or cerebral redistribution admitted to the neonatal intensive care unit were included in the trial.Out of the neonates eligible for inclusion ,5 neonates were excluded due to significant haemodynamic instability requiring inotropic support, 2 were excluded as they had inadvertently received enteral feeding prior to randomization. Enrollment of the infant, recording of the baseline information and randomization was done by investigators once written informed and signed consent was obtained. The randomization codes were generated by an internet website randomnumbergenerator.org. These codes were placed in sequentially numbered opaque sealed envelopes. Infants were assigned randomly either to early or to late feeding group with the use of these sealed envelopes. The randomization method used was stratified, balanced block procedure for two gestational age strata :less than 32 weeks and more than 32 weeks. Blinding of intervention and outcome measurement could not be done as the NICU staff had to access the plan for patient management.

Data collection included birth weight, gender , mode of delivery and need for resuscitation at birth, type of Doppler abnormality. Gestational age was calculated based on mothers last menstrual period and or early pregnancy ultrasound scan or New Ballard score.

Infants were treated as per NICUs standard protocol for management for preterm and low birth weight neonates. All infants who were less than 32 weeks were started on caffeine citrate within the first 24 hrs of life. Infants were put on respiratory support and received surfactant if indicated by severity of RDS. The patients were started on feeds after completion of day 2 or day 6 according to their group. The milk given was in the form of expressed breast milk only,either mothers own milk or donor milk, the feeds were advanced at rate of 20ml/kg/day in babies below 1500g or at 30ml/kg/day in babies above 1500g.Babies were given partial parenteral nutrition through peripheral intravenous line till achievement of feeds upto 120ml/kg/day ,thereafter fluids were discontinued and feeds were advanced.

The decision to temporarily withhold feeds or deviate from the feeding schedule in any particular case was taken, because of apparent feed intolerance or clinical deterioration, at the local clinician's discretion. Gastric residuals are not uncommon in preterm infants. As long as the infant was well and had no abnormal abdominal signs enteral feeds were continued when gastric aspirate was 2-3 ml or less (2 ml in a baby of less than 750 grams birth weight). After any withholding of feeds, depending on patient condition feeds were again restarted from day 1, or the volume previously tolerated then increase as scheduled daily, or after one or more days at a certain volume increased as scheduled.

Outcomes recorded were time taken to achieve full enteral feeding and incidence of NEC. Secondary outcome measures of death before hospital discharge, duration of hospital stay, duration of parenteral nutrition, occurrence of complications like sepsis, gastrointestinal perforation, gastrointestinal surgery, cholestasis (defined as >2 mg/dl conjugated fraction of serum bilirubin),patent ductus arteriosus requiring pharmacological or surgical treatment, cranial ultrasound abnormality and type of milk at discharge were noted.

Data collection

Data was collected at trial entry, during the infant's stay in the neonatal unit, and at discharge. At trial entry baseline data and eligibility information was collected and documented. Information collected during the infant's stay in the neonatal unit included enteral feeding history and other significant complications.

Statistical analysis:

Statistical analyses was performed with the use of Graphpad InStat software for Windows for the primary and secondary outcomes. Baseline characteristics and outcome measures on continuous scales were analysed by using two sample *t* test or Mann Whitney *U* test as appropriate. Baseline characteristics and outcome measures on nominal scales were analysed by Chi square test or Fisher exact test as appropriate. Statistical significance was considered if *p* value was <0.05.

Sample size calculation for this study was based on rates of admission of babies with abnormal dopplers in the previous 12 months in our NICU. The study was approved by the institute ethics committee before the commencement of trial.

RESULTS

We enrolled 32 preterm neonates with antenatal Doppler reports suggestive of absent or reversed end-diastolic flow or cerebral redistribution.16 were randomized to early feeding and 16 to late feeding group. The mean gestation was 32.5(S.D 2.18 weeks) and mean birth weight was 1138.78 grams(S.D 262.86). The frequency of LSCS delivery, type of Doppler abnormality, need for respiratory support were similar in both groups. All baseline characteristics were comparable in both early and late feeding groups.(Table 1)

The rates of development of NEC was 1(6.25%) in early feeding and none in late feeding group but was statistically not significant(P= 0.29).

The time taken to attain full enteral feeds was significantly less in

early feeding as compared to late feeding group (11.867 +/- 6.37days vs 15.467 +/- 5.69days,p=0.0031).

The number of babies who died during the trial were 3 (9.3%) but the difference between the two groups was not statistically significant. There was no statistically significant difference between the two groups in terms of developmennt of sepsis, PDA requiring treatment and other complications.

In less than 32 weeks strata there were 6 babies in early feeding and 3 babies in late feeding group. In subgroup analysis there was no significant difference between the two groups.

Discussion:

This trial was modelled after the ADEPT trial which compared the clinical course and outcomes between the early feeding and late feeding group. In our study, one patient in the early feeding group developed NEC .Difference between the two groups was statistically insignificant.. There was statistically significant benefit in early feeding group in terms of duration of parenteral nutrition and time taken to achieve full feeds. This translated into lesser time towards discharge in the early feeding group which was statistically significant, after excluding the patients with exceptionally prolonged hospital stay due to congenital CMV infection in one case and CNS abnormality requiring prolonged respiratory support in the other case.

In the ADEPT (abnormal Doppler enteral prescription trial) trial conducted by Leaf A et al, 404 patients were randomly assigned from 54 hospitals in the United Kingdom and Ireland (202 to each group). Median gestation was 31 weeks. Full, sustained, enteral feeding was achieved at an earlier age in the early group: median age was 18 days compared with 21 days (hazard ratio: 1.36 [95% confidence interval: 1.11–1.67]). There was no evidence of a difference in the incidence of NEC: 18% in the early group and 15% in the late group (relative risk: 1.2 [95% confidence interval: 0.77–1.87]). Early feeding resulted in shorter duration of parenteral nutrition and high-dependency care, lower incidence of cholestatic jaundice, and improved SD score for weight at discharge.

In our study, the mean gestation and birth weight were comparatively higher with a mean gestation of 34 weeks and mean birth weight of 1270g.As all the preterm neonates with abnormal Doppler delivered in our institution were considered for enrollment, this may be due to difference in our obstetric practices with reluctance to electively deliver before 32 weeks of gestation in situation of questionable survival. Also it may be due to late detection and referral of mothers with PIH from peripheral centers with later referral of such mothers.

At times mothers with severe PIH are referred with serious maternal complications and they are delivered for maternal indications before there is time to obtain a Doppler study which takes time due to a busy ultrasonography department. Hence some severely growth retarded babies who may have had Doppler changes were not detected and hence could not be included in the trial.

Overall only 7 extremely low birth weight babies were included in the trial. No babies were below 29 weeks of gestation were included in comparison to ADEPT trial where atleast 20% of the patients were less than 29 weeks of gestation and 50 % of the patients were ELBW neonates. Overall 4 patients required resuscitation at birth.

Overall 3 patients died before attaining full enteral feeds.1 in the early feeding group and 2 in the late feeding group. All the 3 patients who died before in the duration of the trial were extremely low birth weight neonates. The single death in the early feeding group was related to NEC and late onset sepsis. Difference in between the groups was not statistically significant.

The rates of development of NEC were 1 (6.25%) in early feeding and none in late feeding group but was statistically not significant(P= 0.29). The overall rate of development of NEC/septic ileus in the ADEPT trial was 19.8% without any significant difference between the early feeding and late feeding group.

One patient in our study underwent GI perforation due to NEC requiring insertion of a glove drain.The patient had a birth weight of 740 grams. Exploratory laparotomy could not be performed due to unstable condition of the patient. This patient died at 50 days of age due to NEC and late onset sepsis. No patient developed cholestasis as compared to the ADEPT trial in which around 5% of the patients developed these complications. This may be due to the fact that patients in our study were of comparatively higher birth weight and gestational age than the patients in ADEPT trial.

Higher number of patients (10) in the early feeding group developed feed intolerance requiring temporary withholding of feeds, as compared to fewer patients with similar problems (5) in the late feeding group. However, this difference was not statistically significant. The incidence of feed intolerance did not seem to interfere with eventual time taken to achieve full feeds in these patients.

The overall number of patients developing sepsis which required treatment was disturbingly high with 7 out of 16 in late feeding group requiring treatment for sepsis ,and 2 patients out of 16 in the early feeding group developed sepsis. The difference in incidence of sepsis between the groups, even though there were more cases in the late feeding group,was not statistically significant. Among the deaths sepsis was the main cause in all the 2 out of 3 deaths. As in comparison with the general NICU population, the incidence of sepsis appears to be more in these patients, it has to be seen whether these babies have increased susceptibility to sepsis as compared with other preterm babies with normal Doppler studies. This could be a research question in the future for the Indian set-up.
The time taken to attain full enteral feeds was significantly less as compared to late feeding group (11.867 +/- 6.37days vs 15.467 +/- 5.69days,p=0.0031).

The duration of parenteral nutrition was significantly less in early feeding as compared to late feeding group (10±5.49days vs 15.17±6.53 days, p=0.001).

The duration of hospital stay was significantly less in early feeding as compared to late feeding group (18.53±10.5days vs 21±13.2 days, p=0.0147).

Thus early feeding appears to be better for these high risk babies. Reaching full feeds earlier will reduce the need for intravenous drips and infusions and reduce number of interventions and risk of sepsis in the babies .Earlier discharge home noted in the early feeding group will only free up cot space but it also means that the whole family can benefit as the emotional and financial stresses will be reduced.

What is known:

- Preterm neonates with absent or reversed flow velocities in the antenatal Doppler are at increased risk of development of NEC due to impaired gut perfusion.
- Late initiation of feeds is often practised to lessen the risk of GI complications,bbut this practice increases the duration of time required to reach full feeds.

What this study adds:

- Early feeding initiation and increase as per protocol in preterm neonates with absent or reversed flow velocities in the antenatal Doppler reduces the duration of time required to reach full feeds, while no increase in the overall complication rate such as NEC is noted.

Table 1: Comparison of baseline characteristics between early and late feeding group

Baseline Characteristics	Early feeding (n=16)(50%)	Late feeding (n=16)(50%)	P value
Birth Weight(g) (Mean±SD)	1119±181.26	1116±181.26	0.65
Gestational Age(wks) (Mean±SD)	32.18±2.07	32.81 ±2.31	0.52
Male	8(50%)	5(31%)	0.47
Cesarean delivery	15	15	1.5
Need for Resuscitation	4	0	0.04
Type of Doppler abnormality	ADF=10,REDF=6	ADF=11,REDF =5	1.00

Table 2: Comparison of incidence of NEC between early and late feeding group

Primary Outcomes	Early feeding (n=16)(%)	Late feeding (n=16)(%)	Relative risk	P value
Incidence of NEC	2(12.5)	3(18.75)		0.29

Table 3: Comparison of secondary outcomes and complications between early and late feeding groups

Secondary Outcomes	Early feeding (n=31)(%)	Late feeding (n=32)(%)	Relative risk	P value
Death before discharge	1(6.45)	2(12.5%)	0.644	0.5
Sepsis	2	7	0.365	0.056
PDA	1	3	1.615	0.14
Cholestasis	0	0	-	-
GI perforation	1	0	2.06	0.5
Feed intolerance	10	5	1.889	0.07
Cranial usg abnormalities	1	1	1.00	0.75

Table 4: Comparison of time taken to attain full feeds, duration of hospital stay and parenteral nutrition outcomes between early and late feeding groups

	Early feeding	Late feeding	P value
Time for reaching full feeds	11.867 +/- 6.37days	15.467 +/- 5.69days	p=0.0031
Time on iv fluids	10±5.49days,	15.17±6.53 days	p=0.001
Duration of hospital stay	18.53±10.5days	21±13.2 days	p=0.0147

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