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Incidence of Feeding Intolerance and Necrotizing Enter Colitis in Preterm Growth-Restricted Neonates with Abnormal Antenatal Doppler Studies.

Mohamed Abdelmaaboud [1*], Ashraf Eissa[1], Ahmed F Eldakrouri[1] and Abdelbaset Mohammed[2]

[1]*Departments of Pediatrics, NICU*

[2]Obstetrics and Gynecology Hammad Medical Corporation,Qatar

[*]**Corresponding author:** Mohamed Abdelmaaboud, Departments of Pediatrics, NICU; Email: dr_mohamed318@hotmail.com

Abstract

Background: Preterm and growth-restricted babies are at high risk of feeding intolerance and necrotizing enterocolitis, as well as post-natal growth failure.

Objective: To evaluate the effects of an "early" enteral feeding regimen, starting on day 2 after birth compared to late enteral feeding, starting on day 6 after birth in preterm growth restricted babies with abnormal antenatal Doppler studies regarding the incidence of NEC and feeding intolerance.

Patients and Methods: Babies with gestational age below 37 weeks, and with birth weight below 10th centile for gestational age, selected and sub classified into an "early" or "late" enteral feeding regimen.

Results: Hundred-thirty three infants selected for the study: 66 received early feeding and 67 received delayed feeding. The incidence of NEC and feeding intolerance was not significantly different between the two groups.

Conclusion: Early minimal enteral feeding (MEF) of preterm infants with IUGR and abnormal antenatal Doppler results may not have a significant effect on the incidence of NEC or feeding intolerance.

Key words:

Minimal Enteral Feeding; IUGR; Necrotizing Enterocolitis; Abnormal antenatal Doppler

Introduction

Antenatal ultrasound with Doppler assessment of fetal blood flow velocities has made it possible to detect a population of fetuses with poor growth and abnormal circulation. Absence or reversal of end diastolic flow (AREDF) in the umbilical artery is associated with poor outcome and thus elective premature delivery is common [1]. Those preterm infants are at increased risk of adverse neonatal outcomes. Absence or reversal of end diastolic flow phenomenon occurs in approximately 6% of 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 restriction (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 [3]. 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 [4]. 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 [5].

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 necrotizing enterocolitis (NEC) [1]. Necrotizing enterocolitis is the commonest serious gastrointestinal emergency in neonatal intensive care units (NICU) and is associated with a high mortality and morbidity [6]. Extreme prematurity is the greatest risk factor, and whilst the specific etiology is often not clear in individual babies, under perfusion and/or hypoxia of the gut are thought to be important predisposing factors. Enteral feeding and bacterial invasion are commonly associated factors. Reduced gut blood flow due to splanchnic vasoconstriction [1] may cause hypoxic-ischemic damage to the intestine or its mucosa predisposing to NEC. Additionally, these conditions may affect normal motor, secretory and mucosal development so that the intestine is more susceptible to stasis, abnormal colonization and bacterial invasion postnatally. IUGR is associated with bone marrow suppression and neutropenia in early postnatal life, which may also increase susceptibility to infective factors [7].

There is no consensus regarding how best to prevent NEC and feeding intolerance 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 [8]. The timing of introduction and rate of progression of milk feeds is an area of clinical uncertainty with arguments in favor of both early and late introduction of enteral feeds. Early introduction may improve nutrition and growth, but may increase the risk of NEC and feeding intolerance [9]. 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 and may not reduce the incidence of NEC [10]. Prolonged use of parenteral nutrition increases the risks of sepsis, cholestatic jaundice and vitamin and mineral deficiencies [11]. Growth restricted infants are at particularly high risk of parenteral nutrition-related liver disease [12].

The use of minimal enteral nutrition (MEN) (trophic feeds, gut-priming, non-nutritive feeding) has increasingly been used in the early feeding of preterm infants and appears to be well tolerated and beneficial in terms of gut motility, earlier establishment of substantive milk feeding and reduced cholestasis but increased risk of NEC could not be excluded [13-19].

Therefore, this study was conducted to evaluate the effects of an early minimal enteral feeding regimen, starting on day 2 after birth

compared to late minimal enteral feeding, starting on day 6 after birth in preterm growth restricted babies with abnormal antenatal Doppler studies regarding the incidence of NEC and feeding intolerance.

Patients and Methods:

This retrospective study was conducted in Women's Hospital, Hamad Medical Corporation (HMC) From January 2009 to March 2012 after being accepted by the local research committee. One hundred and thirty-three preterm growth restricted babies were selected for the study from those admitted to NICU with the following criteria:

(1) A gestational age ranging from 24 – 36+6days weeks (based on clinical dating or early ultrasound)

(2) Small for gestational age (birth weight < 10th centile for gestational age based on Child Growth Foundation Charts [20]

(3) Antenatal ultrasound showing IUGR with AREDF on at least 50% of the Doppler waveforms from the umbilical artery on at least one occasion during pregnancy and an evidence of 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 [21]

(4) Arterial cord blood pH ≥ 7.0, base deficit ≥ -12 mmol/L and (5) 5-minute Apgar score > 5.

Neonatal clinical assessment data, routine investigations, demographic and clinical maternal data were reviewed. Clinical management of all selected babies included intravenous parenteral nutrition (glucose, amino acids and intralipid) by the second day after birth for all babies. All other aspects of care were according to local routine practice. Then, the selected babies were subdivided into either early (Group I) or late (Group II) minimal enteral feeding regimen. Babies in group I received minimal enteral feeding in day 2 after birth while those in group II received late minimal feeding on day 6 after birth. Babies in both groups will start feeding based on internal protocols used in NICU, Women's Hospital, Hamad Medical Corporation (HMC).

Initial volume of minimal enteral feedings did not exceed 10-20 ml/kg/day (1-3 ml/kg/feeding). Breast milk was the milk of choice for feeding and if not available neonatal infant formula was used. Neonatal formula (special 24 Kcal) was given for infants with gestational age less than 34 weeks or weight < 2 kg. Neonatal formula (20 Kcal) was given for infants with gestational age more than 34 weeks or weight > 2 kg. Breast milk fortification was considered if additional nutritional support was required once the baby is tolerating around 100 ml/kg/day (breast milk was fortified to 22 kcal/oz) or when tolerating full milk feeds of ≥ 150 ml/kg/day (breast milk was fortified to 24 kcal/oz) .

The feeding protocol of each group was followed regardless of the type of milk available, ventilation status or presence of an umbilical artery catheter (UAC) unless specifically requested by the neonatologist. The decision to withhold feeds or deviate from the feeding protocol because of apparent feeding intolerance or clinical deterioration was depending on the neonatologist decision.

Definition of feeding intolerance in selected patients

Gastric residual was checked before each feed and feeding intolerance was diagnosed based on these findings:

Non-bilious residuals

If gastric residual is 25-50% of the previous feed and the infant has any other worrisome findings, feeding was held.

If gastric residual > 50% of the previous feed or are progressively increasing in volume and/or abdominal girth increased > 2cm in 24 hour – feeding was held and the infant is closely observed.

In the previous 2 conditions feeding was resumed after 24-36 hours started with ¼ previous volumes for 12 hrs then ½ for 12 hrs then full volume as before if the baby tolerated feeds.

Bilious residuals (serious sign)

Feeding was held, close clinical observation, sepsis work up, abdominal x-ray, parenteral antibiotics, and surgical consultation

C) Blood in stools, loose stool, metabolic acidosis and other signs of feeding intolerance, patient was kept NPO and evaluated for NEC.

In the previous 2 conditions re-introduction of feeding depends on the underlying condition and the individual preferences of the supervising Attending Physician.

Necrotizing enterocolitis (NEC) was diagnosed based on modified Bell´s Staging Criteria [22].

The primary outcome measures in this study were age in days at which full enteral feeding (150-160 ml/kg/day) sustained for 72 hours was reached, NEC, and feeding intolerance. The secondary outcome measures were death before hospital discharge, duration of hospital stay, and duration of parenteral nutrition.

Sample Size and Data analysis

A total of 133 patients were collected during study duration. Data were collected; tabulated and statistical analysis was done using SPSS software version 11. Numerical data were represented as number and percent or mean ± SD when appropriate. Categorical variables were compared by chi-square test. Continuous variables were compared by t test or by Mann-Whitney U test based on their distribution. A p value <0.05 was considered statistically significant.

Results

One hundred and thirty three preterm growth restricted infants with abnormal antenatal Doppler studies were collected for this study. They were subdivided to either early minimal enteral feeding (Group I, N= 66) who received feeding on day 2 of life or late minimal enteral feeding (group II, N=67) who received feeding on day 6 of life. There was no significant difference between the two groups regarding different maternal demographic and clinical characteristics including age, nationality, parity, mode of delivery, incidence of preeclampsia and antenatal steroid exposure (Table 1).

Also there was no significant difference between the two patient groups regarding demographic and clinical characteristics of neonates including gestational age, gender birth weight and ventilation days (Table 1).

Variable	Group 1Early feeding day 2 (N=66)	Group 2Late feeding Day 6 (N=67)	P-value
Maternal age (years)	26.6±3.2	28.3±7.1	NS
Nationality (N %) Qatari Non-Qatari	28 (42.4%) 38 (57.6%)	29 (43.3%) 38 (56.7%)	NS
Parity (N %) Primigravida Multigravida	39 (59.1%) 27 (39.9%)	36 (53.7%) 31 (46.3%)	NS
Mode of delivery (N %) Cesarean section Vaginal delivery	57 (86.3%) 9 (13.7%)	60 (89.5%) 7 (10.5%)	NS
Preeclampsia (N %)	18 (27.3%)	16 (23.9%)	NS
Antenatal steroid exposure (N %)	48 [72.7%]	52 [77.6%]	NS
Gestational age (wk) (Mean±SD)	32.5±3.5	31.8±2.9	NS
Birth wt in gm (median and range)	740 (620–1270)	810 (630–1945)	NS
Gender Male (N %) Female (N %)	30 (45.2%) 36 (54.8%)	33 (49.2%) 34 (50.8%)	NS
Mechanical ventilation	47 (71.2%)	35[52.2%]	NS
Where, SD: Standard Deviation; N: Number; NS: Non significant; Gm: gram; wk: week			

Table 1: Demographic and clinical Characteristics of mothers and their preterm IUGR babies in both groups

The primary and secondary outcome measures in the two groups are reported in (table 2).

Variable	Group 1 Early feeding day 2 (N=66)	Group 2 Late feeding Day 6 (N=67)	P-value
Days to reach full feeding Median Range	18 (11–46)	20 (12–25)	NS
Days to regain birth weight MedianRange	14 (8–25)	13 (9–28)	NS
Feeding intolerance (N %)	24 (36.4%)	25 (37.3%)	NS
Necrotizing enterocolitis (N %)	9 (13.6%)	7 (10.4%)	NS
Length of Hospital stay Median Range	23 (6–60)	30 (3–109)	NS
Where, N: Number and NS: Non significant			

Table 2: Outcome measures in the two groups

There was no significant difference between the two groups regarding different outcome measures including days to reach full feeding, days to regain birth weight, feeding intolerance, NEC and length of Hospital stay. Out of 133 infants, 16 (12.1%) presented with NEC and 31 (23.3%) presented with feeding intolerance as shown in (Table 2).

An analysis was performed to identify the potential relationship between NEC and significant perinatal parameters (Table 3). Neonates

with NEC were delivered at significantly earlier gestational age and at lower birth weights (p 0.02 and p 0.005, respectively).

Variable	NEC (N= 16)	No NEC (N= 117)	P-value
Gestational age (weeks) Median Range	29 24-36	32.2 24-36	< 0.05
Birth weight (gm) Median Range	890 560–1815	1100 790–1935	<0.01
Gender (N %) Male Female n (%)	8 (50%) 8 (50%)	60 (51.2%) 47 (48.8%)	NS
Apgar score at 5 min Median Range	8 6-9	9 8-10	NS
Arterial cord blood pH (Mean ±SD)	7.36 ± 0.14	7.38 ± 0.16	NS
Arterial cord blood base defici Median Range	-0.5 -1.5 - 2.9	-0.7 -1.8 - 2.6	NS
Neonatal deaths (N %)	6 (37.5%)	5 (4.3%)	<0.001
Maternal preeclampsia	5 (31. 25 %)	29 (24.8%)	NS
Antenatal steroid exposure	11 (68.7%)	89 (76.1%)	NS
Where, SD: Standard Deviation ; N: Number; NS: Non significant			

Table 3: Relationship between NEC and perinatal parameters

Discussion

Several mechanisms, acting both before and after delivery, may explain the excess of NEC and feeding intolerance seen in preterm growth restricted infants who exhibited abnormal fetal Doppler. [24, 25] The combination of antenatal and persisting postnatal disturbances of gut perfusion, interacting with the metabolic demands of feeding, may adversely affect intestinal tissue oxygenation, combining with stasis and immunological factors to contribute to the development of NEC and feeding intolerance. In infants with AREDF, the recovery of parameters of intestinal perfusion during the first week provides a sound rationale for a modest delay in enteral feeding in these infants, to ensure that the metabolic stress of feeding is only imposed when baseline intestinal perfusion is as healthy as possible [26].

Although feeds are commonly delayed in high risk infants, there is little evidence that this approach is beneficial. Parenteral nutrition is usually used as an alternative source of carbohydrate, amino acids, and lipid, but side effects are common, especially catheter related sepsis, which occurs in up to 40% of preterm infants receiving parenteral nutrition through a percutaneous central catheter.[27] Other important side effects include cardiac tamponade, drug administration errors, cholestasis, osteopenia of prematurity, and metabolic complications. [28-29]

Due to the previous debate whether early or late feeding is preferred we conducted this study.

Minimal enteral feeding is an alternative approach to delaying feeds is to start small volumes of milk (10–20 ml/kg/day) and continue this for a period of time before advancing the volume of each feed. This approach, known as minimal enteral feeding (MEF), has recognized benefits, including enhanced endocrine and exocrine hormonal activity, improved growth of intestinal mucosa, and maturation of gut motility. [30]

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 [31] who studied 42 infants, seeing only one case of NEC in the unfed group and with McClure and Newell [32] who studied 100 infants, seeing one and two cases of NEC in trophic and control infants respectively.

The trial of Schanler et al [33] contained 171 infants, with 13 cases of NEC in the trophic group, compared with 10 cases in the control infants. Combining these results with those of the meta-analysis of Tyson and Kennedy [34], 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). This also is in agreement with the results of the present study. Furthermore, although not the primary outcome of this study, birth weight and gestational age were found to be significant risk factors for the development of NEC, irrespective of the timing of MEF introduction. These results are in agreement with Karagianni et al 2010. [35] On the other hand, in infants in the present study markers of asphyxia including Apgar score at 5 minutes, umbilical cord PH and base excess were not proved to be significant risk factors for the development of NEC and feeding intolerance but this result may be biased as we already excluded known cases of birth asphyxia. This was in agreement with the results of Neu 2005 and Simuunek 2008. [36, 37] Moreover, maternal preeclampsia did not prove to be a risk factor for the development of NEC and feeding intolerance in the present study. In contrast, a previous report in preterm, very low-birth-weight infants demonstrated a significant association between maternal hypertensive disorders and the development of NEC [38]. The authors speculated that the reduced uteroplacental blood flow in preeclampsia may result in birth asphyxia with redistribution of blood flow, bowel ischemia, and NEC [39]. Also pregnancy induced hypertension with fetal growth restriction is also associated with neutropenia in early postnatal life, which may affect susceptibility to infective factors which affect the outcome of preterm babies with IUGR. [40]

In this study prenatal steroid exposure had no effect on the incidence of NEC and feeding intolerance, this may be explained by the fact that most of mothers of patients recruited in the study received antenatal steroid, this is in agreement with some previous studies. [37, 41-44]

This study concluded that early introduction of MEF in preterm growth restricted infants with abnormal antenatal Doppler results has no significant effect on the incidence of NEC or feeding intolerance. Furthermore, birth weight and gestational age were found to be significant risk factors for the development of NEC and feeding intolerance, irrespective of the timing of MEF introduction. However, because of the relatively small sample size, 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.

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