Feeding Intolerance in Preterm Infants Fed with Powdered or Liquid Formula: A Randomized Controlled, Double-blind Pilot Study

Lena Ignacio, Khalid AlFaleh
King Khalid University Hospital, 'Department of Paediatrics, King Saud University, Riyadh, Saudi Arabia. E-mail: dr.lena39@gmail.com

CONTEXT
Feeding preterm neonates is one of the main challenges faced by neonatal practitioners on daily basis most specifically those in the low birth weight groups. Breast milk when available is always the best especially during the 1st week of life. However, in cases when human breast milk is not available or is inadequate, choosing the next best substitute formula that would be well tolerated could prove to be trying.

It had been a standard practice worldwide to use the liquid or ready to feed milk formulas. This was brought about by the many reported outbreaks of neonatal sepsis, gastroenteritis, and Necrotizing enterocolitis (NEC) due to the bacterial contamination of powdered formulas during preparation in hospitals or Neonatal Intensive Care Unit (NICU) settings in developed countries. But is the liquid formula really the right choice for supplementing breast milk in feeding these high risk neonates?

MATERIALS AND METHODS
Single-center prospective, randomized and controlled, double blinded pilot study which was conducted from July, 2010 to December, 2011 in a University Hospital in Ankara, Turkey.

Population
Inclusion
Preterm infants (gestational age less than 37 weeks) admitted to NICU after birth and for whom at least 75% of daily enteral nutrition volume was supplied as preterm infant formula from the first day of life because of complete absence or inadequate amount of maternal breast milk.

Exclusion
1. Those who are at high-risk of developing feeding intolerance or NEC such as infants with intrauterine growth restriction or who were small for gestational age
2. Infants with perinatal asphyxia
3. Neonates who had prenatal hemodynamic disturbances such as diminished, absent or reversed umbilical artery Doppler flow velocimetry
4. Presence of congenital or chromosomal abnormalities
5. Those infants with inherited metabolic diseases, early or late onset sepsis, and those with hemodynamically significant patent ductus arteriosus requiring medical or surgical treatment
6. Infants who were given exclusive or predominantly (more than 75% of enteral feeding volume) breast milk in the 1st week of life.

Intervention
Eligible Infants were prospectively and randomly assigned to receive the same non-hydrolyzed cow's milk based preterm formula in powdered or liquid (ready to feed) form.

Outcomes
Primary
Incidence of feeding intolerance in preterm infants where feeding intolerance was defined as the presence of at least three of the following criteria:
1. Gastric residual volume of more than 50% of the previous feeding volume
2. Emesis (at least 50% of the previous feeding volume)
3. Abdominal distension
4. Absence of occult blood in stool.

Any infant with gastrointestinal signs and “positive occult blood in the stools” was evaluated as NEC stage I.

**Secondary**

Fasting and postprandial gastric pH.

**Allocation**

Randomization was performed by the chief dietician of the hospital using sealed opaque envelopes.

**Blinding**

The investigators, medical staff and parents were blinded to which formula the infants were to receive.

**Formula preparation and concealment**

The powdered formulas were reconstituted and prepared in the centralized formula room of the hospital by boiling drinking water and then cooled to 40°C in standard 250-ml glass bottles which were previously sterilized at 120°C. Liquid formulas were poured into the same standard 250-ml glass bottles to provide identical appearance.

All these bottles containing either reconstituted powder or liquid formulas were covered with aluminum foil in order to prevent recognition of the difference in the color of the formula (powdered formulas are white whereas the liquid formulas are light brownish to beige). All bottles were sent to NICU in closed transports and kept in refrigerators at 2°C-8°C until use.

**RESULTS**

The study was completed with a total of 78 preterm infants out of the 135 who were considered eligible and were initially randomized to one of the study groups. Forty four of those who completed the study received powdered formula whereas 34 were assigned to the liquid formula group. The mean birth weight was 1,800 g. There were no differences in baseline characteristics, risk factors and presence of neonatal morbidities in both groups.

The incidence of feeding intolerance was significantly higher in infants fed with liquid formula (n=34) when compared with infants fed with powdered formula (n=44) (9 (26.5%) vs. 2 (4.5%), P<0.01, respectively). The median fasting gastric fluid pH was significantly lower and postprandial gastric fluid pH was significantly higher than in infants fed with powdered formula (2.9 vs. 3.4, P<0.01 and 6.0 vs. 5.9, P<0.05 respectively). Infants fed with liquid formula regained birth weight significantly later than infants fed with powdered formula (9.5 vs. 8.0 days, P<0.01) [Table 1].

**CONCLUSION**

This is the first randomized controlled, double blinded, pilot study that had shown an increased incidence and delayed growth in preterm infants fed with liquid or ready to feed formula when compared with powdered infant formula of the same brand. Increased incidence of FI and delayed growth in the 1st weeks of life in preterm infants fed with liquid formula might be caused by altered gastric acidity or possible disrupted protein bioavailability due to different production and sterilization processes.

**COMMENTARY**

Although, the study idea is unique and well thought of, several issues and questions could have been raised. It’s not clear why there is a 10 patients’ difference in the numbers of intervention and control groups. Feeding intolerance is a prominent feature of the very preterm infants. Infants included in this study were more mature and had a mean birth weight above 1500 g at birth, which might limit the applicability of their findings. A very important aspect of mixing formula or using the ready to feed form is the risk of contamination when the formula is prepared at the local institutions. The issue of formula surveillance and incidence of nosocomial sepsis was not addressed adequately. Other published small studies showed similar results with increased rate of regurgitation in the ready to feed formula group.[2]

A similar study by Lucas et al. showed that infants fed the reconstituted formula had a larger increase in their body weight compared to ready to feed formula. Errors in mixing powdered formula were thought to play a role. When compared to breast fed infants growth pattern, ready to feed formula showed a more physiological pattern as to powdered formula.[3]

We believe that the findings of this study could encourage...
researchers to perform larger data sets including smaller infants and including hard outcomes that are of interest to both clinicians and parents of preterm infants.

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