Effect of Human Milk Fortification in Appropriate for Gestation and Small for Gestation Preterm Babies: A Randomized Controlled Trial

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Objective: *To study the effects of human milk fortification on short term growth and biochemical parameters in preterm very low birth weight (VLBW) appropriate for gestation (AGA) and small for gestation (SGA) babies.* ***Design:*** *Prospective, randomized controlled trial.* ***Setting:*** *Level III neonatal unit* ***Subjects:*** *Preterm infants weighing ≤ 1500 grams and ≤34 weeks of gestation born between March 2001 to June 2002.* ***Methods:*** *Babies (n =166) were randomized in two groups either to get fortified human milk or exclusive human milk along with mineral and vitamin supplementation when feed volume reached 150 mL/Kg/day. Fortification was done with a powdered fortifier added in expressed breast milk and continued till the baby reached 2 Kg or full breast feeds. Primary outcome measures were Short-term growth (daily weight, length and head circumference (HC) weekly) till discharge or 2 Kg.* ***Results:*** *Fortification (n = 85, birth weight 1202 g, gestation 30.8 wk) resulted in better growth in preterm VLBW babies as compared to control group (n=81, birth weight 1259 g, gestation 31.3 wk). Weight gain (15.1 and 12.9 g/kg/d, P <0.001), length (1.04 and 0.86 cm/week, P = 0.017) and HC (0.83 and 0.75cm/week, P<0.001) increased significantly in fortified group. SGA babies showed significant improvements in weight (16g/Kg/d and 12.9g/kg/d, P = 0.002) and length (1.09 cm/week and 0.92 cm/week, P = 0.042) in fortified group (n = 38) as compared to control group (n = 29). In AGA subgroup, there was significant increase (P = 0.006) in length (1 cm vs 0.82 cm) in fortified group but no difference in weight (P = 0.12) or HC (P=0.054) in fortified (n=47) vs control (n=52) group. Biochemical parameters were comparable, however feed intolerance was more in control group.* ***Conclusion:*** *Preterm VLBW babies showed better growth with human milk fortification. The effect is significant in SGA (weight and length) rather than AGA (only length) babies.*

Keywords: *Feed intolerance, Human milk fortification, Preterm, Small for gestation babies, Very low birth weight.*

POOR postnatal growth of preterm neonates continues to be a major problem. Intrauterine growth retardation is an additional risk factor in the growth of preterm infants. Breast milk is considered as the best food for the neonates due to its several nutritional and immunologic advantages but this has been well established that(1,2) human milk is an inadequate source of protein and minerals for growing premature babies. Very low birth weight babies need higher calories, protein and minerals to achieve adequate catch up growth(3). The need is even higher in growth retarded babies. There are several studies(4-6) showing improved growth and biochemical parameters in the preterm babies who were fed fortified human milk. However, there is no study to assess the effect of fortification on growth of small for gestation babies. In developing countries the incidence of growth retardation is high(7) and with better nutrition a good catch up growth can be expected. The aim of this study was to compare the growth between fortified and unfortified human milk fed preterm and growth retarded neonates.

Subjects and Methods

This prospective randomized controlled study was carried out in the neonatal unit of PGIMER, a tertiary care referral center in North India. Preterm infants weighing ≤1500 grams and ≤34 weeks of gestation born between March 2001 to June 2002 who fulfilled the eligibility criteria (reached feed volume of 150 mL/kg/day and feed constituted at

least 80% breast milk) were enrolled in this study. Babies with major congenital malformation and gastrointestinal abnormalities were excluded. Gestation was assessed from history of last menstrual period and after birth by new Ballard scores(8). Appropriate for gestation and small for gestation was assigned as per local (PGI) intrauterine growth chart.

Primary outcome measures were (*i*) increase in weight, length and head circumference till 2 kg. Secondary outcome measures were (*ii*) biochemical parameters (sodium, calcium, phosphate and alkaline phosphatase till 2 kg), adverse outcomes (feed intolerance NEC), (*iii*) length of hospital stay and (*iv*) morbidities like sepsis, PDA, CLD and IVH.

Babies were randomized into 2 groups using a random number table. The fortified group received a commercial human milk fortifier[Lactodex HMF, Raptakos Brett, Composition of HMF (per 2g sachet to be mixed in 50 mL EBM) protein – 0.2 g, fat – 0.1 g, carbohydrate – 1.2 g, vitamin A –730 i.u, vitamin D – 250 i.u, calcium – 50 mg, phosphate – 25 mg, sodium – 1.75 mg and energey – 6.5 kcal] which was added to the expressed breast milk (EBM) and the control group received EBM along with vitamin and mineral supplementation. Fortification was continued till they reached a weight of 2 kg or the baby achieved full breast feeds.

Babies were weighed daily on an electronic weighing scale (accuracy ± 5g) and head circumference and length measured weekly till discharge or they reached 2 kg on weekly follow up after discharge. Fortification provided additional 19.5 cal/kg/day, protein 0.6 g/kg/day and fat 0.3 g/kg/day per 150 mL/kg/day. Biochemical monitoring included weekly serum calcium, phosphate, alkaline phosphatase and sodium. Side effects were recorded for any feed intolerance (defined as vomiting, diarrhea, abdominal distention, increased aspirates), Necrotising enterocolitis (NEC)-any stage. The other outcomes measured were incidence of chronic lung disease (CLD)- defined as O_2 dependency at 36 weeks PCA, sepsis, intra-ventricular hemorrhage (IVH) grade ≥ 2 and patent ductus arteriosus (PDA). PDA was diagnosed clinically as well as on echo-cardiography.

The primary outcome variable for this study was weight gain (g/kg/day) from the day of enrolment till discharge or 2 kg. A sample size of 32 per group was required to detect a difference of 1.5 g/kg/day in the rate of weight gain (Standard deviation of 6 g/kg/day, an error of 0.05 and power of 80%). Two groups were compared by using student's *t*-test for continuous variables and Pearson's chi-square and Fisher's exact test for categorical variables. Values are expressed as mean and standard deviation. P value of <0.05 was considered significant.

TABLE I– *Baseline Characteristics of Fortified and Control Group*

	Fortified (n = 85)	Control (n = 81)	P
Birth weight (grams)	1202 ± 202	1259 ± 160	0.049
Gestation (weeks)	30.8 ± 2	31.3 ± 1.9	0.17
Apgar (5 min)	8.5 ± 0.6	8.4 ± 0.9	0.319
Oral feeds started (day of life)	2.1 ± 1.7	1.8 ± 1.2	0.22
Full feeds reached (day of life)	9.8 ± 5.3	8.7 ± 4.73	0.17
Weight at enrollment	1189 ± 209	1222 ± 17.3	0.27
Enrolled (day of life)	11.8 ± 5.7	11.1 ± 5.6	0.44
Fluid (mL/kg/day)	168 ± 14.4	168 ± 13.7	0.93
SFD (n)	38	29	0.24
Received ANS (n)	52	51	0.81
Ventilated (n)	30	24	0.43

TABLE II–*Biochemical, Growth and Other Outcome Measures in Fortified and Control Group*

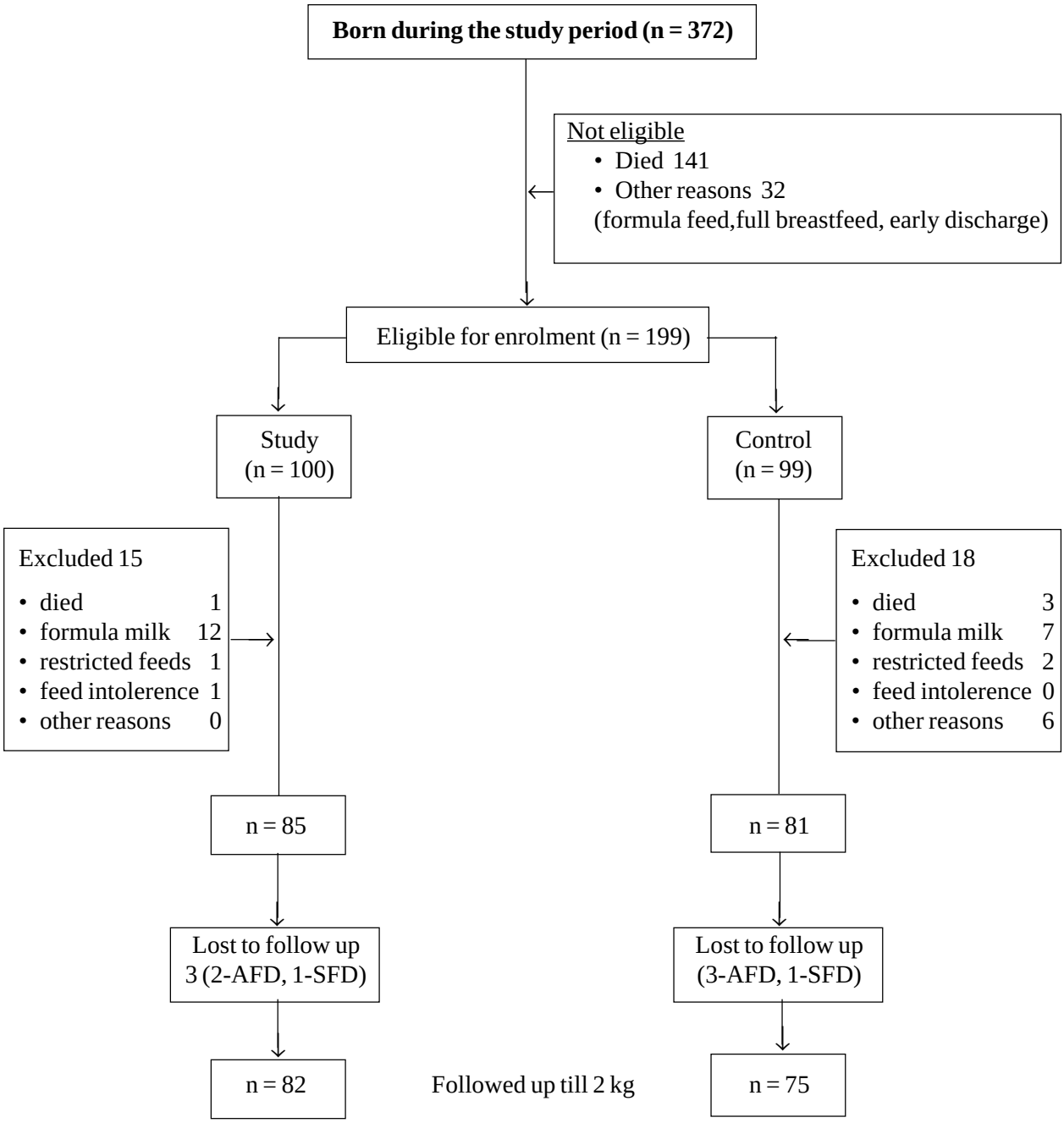
	Fortified (n= 82)	Control (n = 75)	P
Feed intolerance (n)	17	22	0.001
Wt gain (grams/kg/day)	15.1 ± 4	12.9 ± 4	0.00
Length (cm/week)	0.86 ± 0.2	1.04 ± 0.3	0.017
HC (cm/week)	0.83 ± 0.2	0.75 ± 0.2	0.00
Na(meq/L)	135 ± 7.1	136 ± 6.2	0.25
Calcium (mg/dL)	9.56 ± 0.6	9.49 ± 0.7	0.50
P04 (mg/dL)	5.48 ± 1.6	5.62 ± 1.6	0.63
AP (KAU)	37.4 ± 14.1	32.7 ± 13.6	0.57
PDA (n)	9	3	0.14
Sepsis (n)	22	20	0.97
IVH (n)	17	11	0.32
CLD (n)	9	2	0.036
Readmission (n)	5	6	0.08
Hospital stay (days)	31.9 ± 16.2	29.4 ± 13.2	0.27

TABLE III-–*Baseline Characteristics, Growth and Biochemical Parameters in SGA Babies*

	Fortified SGA (n = 37)	Control SGA (n = 26)	P
Birth weight (grams)	1129 ± 192	1217 ± 165	0.054
Gestation (weeks)	31.8 ± 1.7	32.6 ± 1.5	0.067
Weight gain (grams/kg/day)	16.05 ± 3.6	12.97 ± 4.3	0.002
Length (cm/week)	1.09 ± 0.36	0.92 ± 0.3	0.042
HC (cm/week)	0.82 ± 0.2	0.74 ± 0.2	0.157
Na (meq/L)	136 ± 7.5	136 ± 5.3	0.85
Ca (mg/dL)	9.45 ±0.7	9.55 ±0.8	0.66
PO_4 (mg/dL)	5.3 ±1.9	6.1 ±2.2	0.27
AP (KAU)	42 ±13.9	35.2 ±15.2	0.178

Results

The study was approved by Institute research ethics committee and written informed consent was taken from parents of each child. There were 85 babies in the fortified group and 81 in the control group. Thirty eight babies were SGA in fortified and 29 in control group and 47 babies who were AGA in the fortified group and 52 in control group. Eighty two babies in fortified group and 75 in control group completed the study (see details in the flow diagram). Baseline characteristics of fortified and control group were similar (*Table I*). The fortified group had significantly better weight gain (P = 0.001), increase in length (P<0.00l) and head circumference (P = 0.017). In both the groups, serum calcium, phosphate, alkaline phosphatase and sodium were comparable (*Table II*). Duration of hospital stay, incidence of sepsis, IVH, PDA, NEC were similar, however in fortified group, babies had more (P = 0.036) chronic lung disease as compared to control group (*Table III*). No baby developed NEC after randomization.



Outcome in SGA babies: The baseline characteristics were similar. The fortified SGA group (n = 37) had significantly better weight gain (P = 0.002) and increase in length (P = 0.042) as compared to control SGA (n = 26) babies (4 lost in follow up). There was no difference in head growth and their metabolic parameters were comparable (*Table III*). Incidence of sepsis, IVH, PDA, CLD were similar.

Outcome in AGA babies: These babies were comparable for weight and gestation. There were no differences in their weight gain (14.38 ± 4.8 g/kg/day in fortified group *vs* 12.92 ± 3.9 g/kg/day in control group, P = 0.12), though length had increased significantly (1 ± 0.3 cm/week in fortified group *vs* 0.82 ± 0.3 in control group, P = 0.006). Head growth was slightly better (P = 0.054) in fortified group. Metabolic parameters in both groups were comparable. Incidence of sepsis, IVH,

What this Study Adds

- Human milk fortification improves the growth of preterm very low birth weight babies.
- Growth is significantly more in preterm small for gestation babies than appropriate for gestation babies.

PDA were not different though CLD was found more in fortified group.

Discussion

Role of human milk fortification for feeding of premature infants is quite well established. Studies have(9,10) shown benefits in weight gain, linear and head growth though improvement in mineral content is doubtful. Our study also showed the similar results that as a group when preterm babies fed fortified human milk they had better weight, length and head growth than control group but on subgroup analysis we found that SGA preterm babies fed fortified milk had significantly better growth than fed unfortified milk as compared to AGA babies. In developing countries the incidence of growth retardation is much higher than developed countries. Hence, fortification may be more useful if used in this group. The biochemical parameters were similar probably due to our unfortified group were given adequate calcium and phosphate supplements. There were no increased side effects related to fortification. Increased feed intolerance in controls was most likely related to vitamin and mineral supplements though higher feed intolerance rate was expected in fortified group as osmotic load is quite high with fortification(11).

Agarwal, *et al.*(11) showed that addition of fortifier in expressed milk increased the osmolality upto 392 mOsm/kg as compared to 302 mOsm/kg in breast milk (per 100 mL). In our study higher incidence of CLD in fortified group is unexplained.

In conclusion, though human milk with fortification for preterm babies has been accepted as standard practice in most of neonatal units, our study showed the benefit of fortification predominantly in preterm SGA babies than preterm AGA babies. Hence, fortification may be particularly more useful in SGA babies. As cost remains a major limiting factor in the use of fortifier it can be used selectively in preterm SGA babies rather than all preterm babies.

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