

Biochemical and Clinical Outcomes of Human Milk Fortification in Preterm Infants: A Randomised Controlled Study from a Tertiary NICU

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ABSTRACT

Background: Preterm neonates are vulnerable to protein-energy malnutrition and metabolic complications due to immature physiology and increased nutritional demands. While human milk fortification is known to improve growth, its impact on biochemical markers and clinical safety outcomes remains inadequately explored in Indian NICU settings.

Objective: To evaluate the effects of multinutrient human milk fortification on biochemical markers (Blood Urea Nitrogen [BUN], serum albumin) and clinical outcomes such as feed intolerance, necrotizing enterocolitis (NEC), and duration of hospital stay in preterm neonates.

Methods: A randomized controlled trial was conducted on 72 preterm infants (<37 weeks, <2kg) allocated to a fortified milk group (FG) or unfortified group (UFG). Weekly BUN and serum albumin levels were measured until discharge. Adverse events and duration of hospitalization were also recorded.

Results: The FG demonstrated significantly higher serum albumin levels (3.5 ± 0.3 g/dL vs. 3.0 ± 0.4 g/dL, $p < 0.01$) and optimal BUN profiles. Incidence of feed intolerance and NEC were low and comparable across groups. Median hospital stay was shorter in FG (21 vs. 26 days, $p < 0.05$).

Conclusion: Fortification of breast milk in preterm neonates is biochemically beneficial and clinically safe, supporting its integration in routine NICU protocols.

Keywords: Preterm infant, fortification, serum albumin, BUN, feed intolerance, NEC, randomized trial.

INTRODUCTION

Preterm infants frequently suffer from nutritional deficits that can compromise short- and long-term outcomes. While human milk is ideal for these neonates due to its immunologic and gastrointestinal benefits, it often fails to meet the heightened protein and caloric demands of very low birth weight (VLBW) infants.

To bridge this gap, human milk fortifiers (HMFs) are commonly used in NICUs. Although the effect of fortification on growth is well-studied, less is known about its influence on **biochemical nutritional status** and **clinical safety outcomes** like NEC and feed intolerance—critical concerns in the vulnerable preterm population.

This study investigates the metabolic impact and clinical tolerability of HMF in preterm infants to validate its use in the Indian NICU setting.

MATERIALS AND METHODS

Study Design and Setting

A prospective, open-label, randomized controlled trial was conducted at the Neonatal Intensive Care Unit (NICU) of Basaveshwara Medical College and Hospital, Chitradurga.

Participants

Inclusion Criteria:

- Gestational age <37 weeks
- Birth weight <2 kg
- Stable preterm neonates on full enteral feeds

Exclusion Criteria:

- Mechanical ventilation
- Congenital anomalies
- Formula-fed neonates
- Feed-intolerant neonates at baseline

Randomization

A total of 72 neonates were randomized equally into:

- **Fortified Group (FG):** Received breast milk fortified with Lactodex HMF
- **Unfortified Group (UFG):** Received unfortified expressed breast milk

Intervention

Fortification began when neonates reached 100 ml/kg/day of enteral feeds. BUN and serum albumin were measured at baseline and then weekly using standard clinical chemistry protocols.

Biochemical Outcome Measures

- **Blood Urea Nitrogen (BUN):** Marker of protein adequacy
- **Serum Albumin:** Indicator of protein nutritional status

Clinical Outcome Measures

- **Feed Intolerance:** Defined by gastric residuals >50% of prior feed or abdominal distension/vomiting
- **NEC:** Diagnosed using Modified Bell's Criteria
- **Duration of NICU Stay:** Days from admission to discharge

Statistical Analysis

Data were analyzed using SPSS v25. Independent t-tests and Mann-Whitney U tests were applied. Chi-square or Fisher's exact test was used for categorical outcomes. $P < 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

No significant difference was observed between groups in baseline gestational age, birth weight, or gender.

Biochemical Outcomes

Parameter	FG (Mean ± SD)	UFG (Mean ± SD)	p-value
Baseline BUN (mg/dL)	6.2 ± 1.3	6.1 ± 1.4	0.81
Week 2 BUN (mg/dL)	12.4 ± 2.1	8.9 ± 2.5	<0.01
Baseline Albumin (g/dL)	3.1 ± 0.4	3.0 ± 0.5	0.46
Week 2 Albumin (g/dL)	3.5 ± 0.3	3.0 ± 0.4	<0.01

Interpretation:

Significantly higher BUN and albumin levels in FG at week 2 suggest improved protein metabolism and nutritional status.

Clinical Outcomes

Outcome	FG (n=36)	UFG (n=36)	p-value
Feed intolerance	2 (5.6%)	3 (8.3%)	0.64
NEC (Modified Bell's)	1 (2.8%)	2 (5.6%)	0.55
Median NICU stay (days)	21	26	<0.05

No statistically significant difference in NEC or feed intolerance was observed. Fortified group had a significantly shorter hospital stay.

DISCUSSION

This study reveals that fortification significantly improves biochemical indices of nutritional adequacy without increasing gastrointestinal intolerance or NEC risk.

Higher serum albumin and BUN levels in the FG indicate enhanced protein availability and utilization. These findings are consistent with:

- **Arslanoglu et al. (2010):** Adjustable fortification improves protein intake without adverse metabolic effects.
- **Picaud et al. (2020):** One-third of VLBW infants require additional protein beyond standard fortification to achieve optimal growth.
- **Ergenekon et al. (2017):** Higher BUN associated with improved neurodevelopmental outcomes.

Clinical Safety:

Contrary to concerns about HMF increasing feed intolerance or NEC, our trial showed no significant increase in either complication. This supports findings by Sullivan et al. (2010) and Kuschel et al. (2009), who demonstrated that HMF use does not raise NEC incidence when appropriately used.

NICU Stay:

The reduced duration of NICU stay in the FG is clinically and economically relevant, underscoring HMF's role in accelerating readiness for discharge.

CONCLUSION

Human milk fortification in preterm neonates leads to improved biochemical markers of nutrition and reduces NICU length of stay without increasing adverse events like NEC or feed intolerance.

It is a safe, effective, and essential component of preterm nutritional management in tertiary care NICUs.

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