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Effects of Higher Protein Formula with Improved Fat Blend on Growth and Feeding Tolerance in Preterm Infants: a Double-Blind, Randomized, Controlled Clinical Trial

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Introduction: Preterm formulas containing greater protein:energy ratio are beneficial for non-breastfed infants, since protein is critical for promoting catch-up growth and synthesis of lean body mass. Additionally, formulas containing enriched sn-2 palmitate (sn-2) and reduced medium-chain triglycerides (MCTs) may support better feeding tolerance and nutrient utilization.

Purpose: To evaluate growth, nutritional status, and feeding tolerance of low birth weight preterm infants fed with either experimental formula (EF) containing 3.4g protein/100kcal, 12.5% of total fat as MCTs, and 40.2% of total palmitic acid esterified in sn-2 position, or control formula (CF) containing 2.9g protein/100 kcal, 30% fat as MCTs, and without enriched sn-2.

Table 1: Anthropometry results (mean ± SD) for preterm infants receiving experimental (EF) or control formula (CF)

	n	EF	n	CF	EF – CF Adjusted Means (95% CI)	p-value[1]
Weight gain (g/day) from FEF D1 until D21 (PP)	54	31.80 ± 8.70	56	29.05 ± 7.55	3.31 (0.21, 6.40)	0.037[2]
Weight gain (g/day) from FEF D1 until D21 (ITT)	68	31.44 ± 8.54	74	28.32 ± 8.71	3.09 (0.31, 5.88)	0.030
< 1500 g	32	29.36 ± 6.63	33	24.91 ± 6.04	5.64 (2.16, 9.11)	0.0027
≥ 1500 g	36	33.29 ± 9.65	41	31.07 ± 9.59	1.06 (-3.54, 5.67)	0.6457
Weight gain (g/kg/day) from D1 until D21 (ITT)	68	16.95 ± 3.78	74	15.36 ± 3.61	1.62 (0.36, 2.89)	0.012
Weight-for-age z-score at D21 (ITT)	68	-1.00 ± 0.64	74	-1.10 ± 0.76	0.14 (0.005, 0.27)	0.042[3]
Length-for-age z-score at D21 (ITT)	68	-0.80 ± 0.67	74	-0.83 ± 0.71	0.10 (-0.04, 0.23)	0.144
Head circumference-for-age z-score at D21 (ITT)	68	-0.78 ± 0.63	74	-0.75 ± 0.66	0.07 (-0.10, 0.23)	0.425

CI = Confidence Interval, FEF = full enteral feeding, D1 = study day 1, D21 = study day 21, PP = per-protocol, ITT = intent-to-treat, D35 = study day 35, D79 = study day 79.
[1]P-values are based on superiority testing (margin=0).
[2]Weight gain results analyzed using mixed effect model repeat measurement (MMRM) with covariates gender, gestational age, post-menstrual age, birth weight, weight at enrollment, and weight at FEF D1.
[3]Z-score results analyzed using MMRM with covariates gender, gestational age, post-menstrual age, z-score at baseline, and z-score at FEF D1.

Materials and Methods: Male and female preterm infants with birth weight ≤ 2000g and gestational age ≤33 weeks were recruited from a Neonatal Intensive Care Unit (NICU) at one hospital in Vietnam, and randomized in double-blind manner to receive EF (n = 80) or CF (n = 80) until reaching 3 kg body weight. Differences between groups in weight gain (primary endpoint) from day 1 (D1) of full enteral feeding (FEF) until D21 were evaluated for non-inferiority (margin = –2.5 g/d) and superiority (margin = 0 g/d). Stool consistency was rated on a 5-point scale with higher scores indicating harder stool. Feeding tolerance (including gastrointestinal symptoms and time to reach FEF) and blood / urine biochemistries related to nutritional status were assessed.

Results: Adjusted mean weight gain was 3.1 g/d greater in EF than CF; the lower limit of the 95% CI (0.31 g/d) exceeded both non-inferiority (P=0.0001) and superiority margins (P=0.030). The difference in weight gain was larger among infants <1500g (5.6 g/d; 95% CI = 2.16, 9.11). Faster weight gain in EF (vs. CF) was sustained into the post-discharge phase until D79 (mean difference up to 2.07 g/d). Differences in length-for-age and head circumference-for-age z-scores at D21 between groups were not significant. There was no group difference in the incidence of gastrointestinal disorders (EF = 21 vs. CF = 18 events), spitting-up / vomiting [EF/CF IRR (95% CI) = 0.57 (0.30, 1.09)] during D1 – D21 period, or time to reach FEF [EF = 16 (15, 17) vs. CF = 15 (13, 17) days]. Infants in the EF group tended to have softer stools [EF = 3.2 ± 0.59 vs. CF = 3.4 ± 0.58; P=0.07]. Serum Blood Urea Nitrogen (BUN) levels were slightly higher in EF vs. CF at D21 [adjusted mean (95% CI); EF = 3.10 (2.89, 3.33); CF = 2.64 (2.46, 2.83), P=0.0015], although all BUN values were within normal range (1.1 – 7.5 mmol/L). There were no differences between groups in the incidence of abnormal serum creatinine or urinary urea values. Conclusions: EF containing greater protein:energy ratio, enriched sn-2, and reduced MCTs (vs. CF) is safe, nutritionally suitable, well-tolerated, and improves weight gain of preterm infants, especially those with very low birth weight.