Title: Enteral protein supplementation in critically ill children: a randomized controlled pilot and feasibility study

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Background: Loss of muscle mass due to the metabolic stress in critically ill children can negatively impact outcomes. Therefore, protein requirements in this population are higher than for healthy children. However, the exact dose of protein intake associated with improved clinical outcomes in this population is unclear The aim of this study was to examine the effect of protein supplementation on clinical outcomes and nutritional status in critically ill children on enteral nutrition, and to assess the feasibility of a protein supplementation trial in the pediatric intensive care unit (PICU).

Methods: Three-arm parallel randomized controlled trial (RCT) in critically ill children on enteral nutrition therapy admitted to an academic center PICU. Patients were randomized to 2 intervention groups, i) polymeric or ii) oligomeric protein modules added within 72 hours of admission, in addition to the nutrition therapy prescribed by the staff. The aim was to reach the protein delivery goal by 4 days. The control group received routine nutritional therapy prescribed by the local dietitian. Demographic and clinical characteristics, nutritional status and daily nutritional intake variables were recorded. Nosocomial infection, PICU and hospital length of stay and duration of mechanical ventilation, and mortality were the primary outcomes. The secondary outcomes included nitrogen balance, nutritional status parameters (body mass index (BMI) for age and weight for age, mid upper arm circumference (MUAC), triceps skinfold thickness and bioelectrical impedance, serum albumin, prealbumin, and C-reactive protein), and signs of intolerance to nutritional therapy.

Results: Over 10 months, we screened 260 patients for eligibility and 20 eligible patients were randomized. One patient was lost to follow-up. At baseline, all patients had BMI values, but after the intervention, MUAC was the most feasible variable (BMI N=14; MUAC N=16). Albumin was obtained from 19 patients at baseline (95%) and from 13 patients (65%) after the intervention. Fourteen patients (70%) had prealbumin at baseline and only 9 (45%) after the intervention. Nitrogen balance was available in 13 patients. The intervention groups, compared to control group, achieved higher protein prescription (p=0.011), actual protein intake (p=0.010) and protein adequacy (p=0.030) in the first 5 days after admission. Enteral nutrition was introduced early and advanced in a stepwise fashion according to the PICU protocol. Approximately 78.5% (11/14) of the patients in the intervention groups used protein supplement in the first 5 days of admission, while none of the control group used the protein supplement.

There was no difference between the groups in the rate of predefined adverse effects between 5 and 7 days of admission.

Conclusion: Our preliminary results suggest that a larger RCT designed to assess the effect of protein supplementation on clinical outcomes and nutritional status parameters in critically ill children on enteral nutritional therapy is potentially feasible. Early EN and use of protein supplementation allows protein intake goals to be achieved during acute illness.

Trial registration: Brazilian Registry of Clinical Trials n° RBR-3h4x97

Keywords: Pediatric intensive care units. Enteral nutrition. Protein. Randomized controlled trial. Morbidity. Length of stay.

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Table 1 – Adverse effects and clinical outcomes in included patients

Variables	Polymeric N=6	Oligomeric N=8	Control N=6	p-value
Adverse effects				
After 5 days of admission				
Hydric balance (mL/kg/day)	17.8 (3.48; 25.46)	23.87 (20.55; 32.68)	24.55 (18.35; 31.00)	0.418[1]
EN interruption n (%)	5 (83.3)	4 (50.0)	4 (66.7)	0.447[2]
Abdominal distension n (%)	0 (0.0)	0 (0.0)	2 (33.3)	-
≥ 3 defecations/day n (%)	1 (16.7)	1 (12.5)	1 (16.7)	1.000[2]
After 7 days of admission				
Hydric balance (mL/kg/day)	18.2 (10.6; 23.6)	24.8 (18.3; 27.9)	19.2 (17.9; 34.7)	0.601[1]
EN interruption n (%)	5 (83.3)	5 (62.5)	4 (66.7)	0.837[2]
Abdominal distension n (%)	0 (0)	1 (12.5)	2 (33.33)	-
≥ 3 defecations/day n (%)	2 (33.3)	1 (12.5)	0 (0)	-
Clinical outcomes				
At discharge				
Nosocomial infection n (%)	2 (40.0)	2 (25.0)	2 (33.33)	1.00[2]
Duration of MV (days)	4 (4; 7)	9.5 (4; 13.5)	8.5 (4; 15)	0.687[1]
Hospital LOS (days)	13 (11; 23)	26 (13; 36)	29.5 (15;32)	0.304[1]
PICU LOS (days)	7 (6; 15)	13.5 (8; 26)	10.5 (8; 21)	0.455[1]

[1] Kruskal-Wallis; [2] Fischer; EN: enteral nutrition; MV: mechanical ventilation; LOS: length of stay; PICU: Pediatric Intensive Care Unit

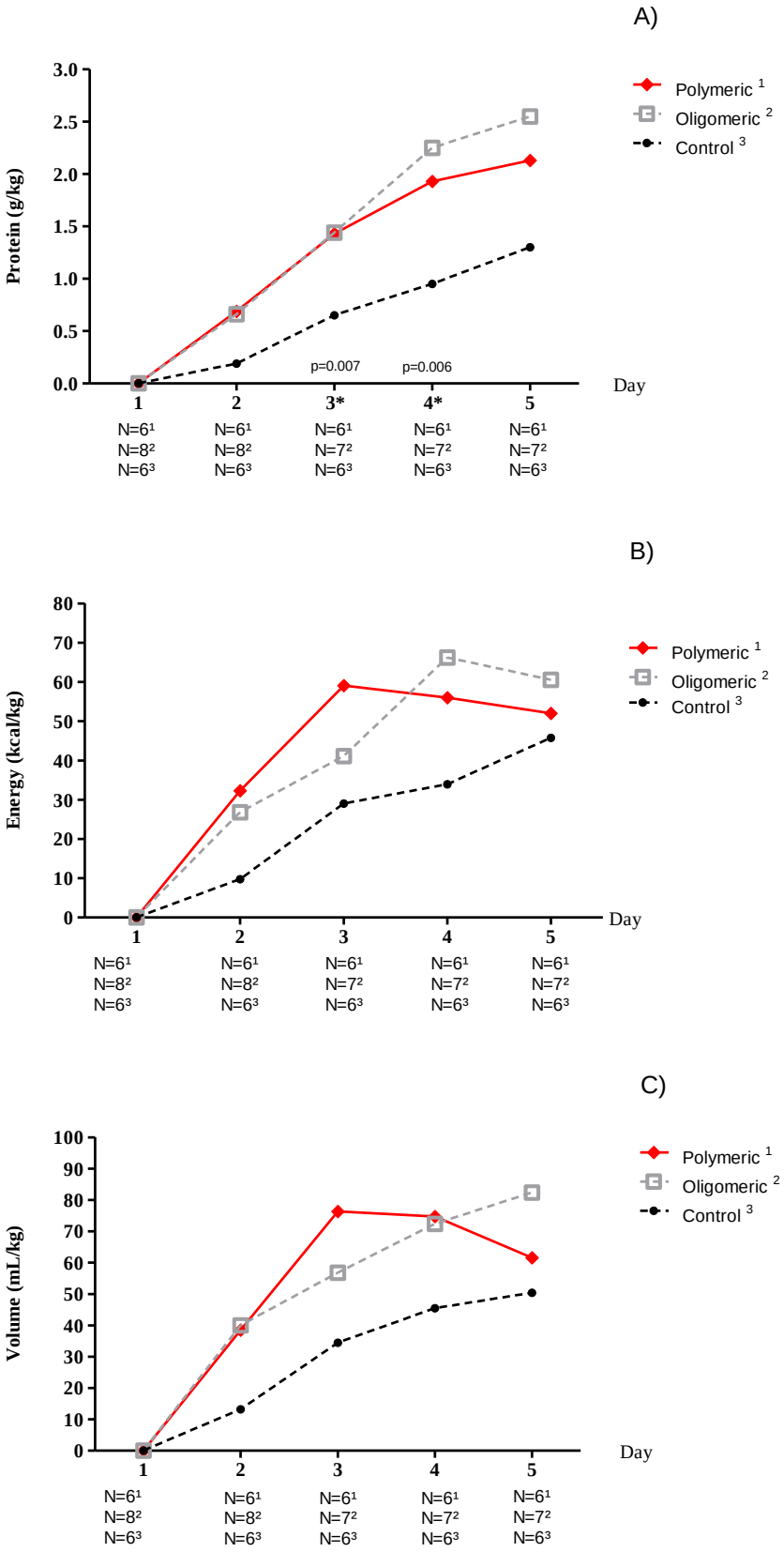

Figure 1 – Median of enteral nutrition intake, stratified by intervention groups, of A) protein (g/kg/day), B) energy (kcal/kg/day) and C) volume (mL/kg/day). Kruskall-Wallis test.