THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives

RESEARCH ARTICLE

An open-label clinical study to evaluate the safety and gastrointestinal tolerance (product compliance) of Groviva® Advance in hospitalized children requiring isocaloric formula for enteral tube feeding

Parag Dekate[1]*, Avinash Reddy[1] , Kalyan Kunchapudi[1]

[1]Complete address: Dept of Pediatrics, Krishna Institute of Medical Science, Hyderabad

*paggy4u@gmail.com

OPEN ACCESS

PUBLISHED
31 July 2024

CITATION
Dekate P., et al., 2024. An open-label clinical study to evaluate the safety and gastrointestinal tolerance (product compliance) of Groviva® Advance in hospitalized children requiring isocaloric formula for enteral tube feeding. Medical Research Archives, [online] 12(7). https://doi.org/10.18103/mra.v12i7.5426

DOI
https://doi.org/10.18103/mra.v12i7.5426

ISSN
2375-1924

ABSTRACT

Objective: This study aims to evaluate the safety and gastrointestinal tolerance of Groviva® Advance in pediatric patients hospitalized in pediatric intensive care units (PICUs) and requiring an isocaloric formula for enteral tube feeding.

Design: This was a prospective five-day single-centre, open-label clinical study.

Methods: The safety and tolerance of Groviva® Advance (45 grams in 170 millilitres of water) were evaluated every day from Day 1 to the end of hospitalization or Day 5, whichever was earlier. The reconstituted amount was 210 millilitres (equivalent to 200 kcal [1kcal in 1ml]) and dosed three hourly (or at the discretion of the pediatrician).

Results: The majority of participants received the Groviva® Advance tube feed three hourly on all five days of the study. The average range of total feeds varied from 295.16 ± 275.19 to 1074.737 ± 347.94 mL per day. Majority of participants had only one episode of loose stools or vomiting, if present, per day. There was minimal or no total daily aspiration or Gastric Residual Volume (>500 ml/day). There was no statistically significant change in weight (p=0.7163) and abdominal girth (p=0.6381) of the study participants. There were no issues encountered during the preparation and administration of Groviva® Advance.

Conclusion: Groviva® Advance was found to be safe and well tolerated by critically ill children admitted to PICUs.

Keywords: Groviva® Advance, enteral tube feed, isocaloric formula, pediatric, critically ill, intensive care unit

Introduction

Malnutrition or undernourishment, defined as a deficient protein: energy ratio, is prevalent in critically ill, mechanically ventilated, or injured children admitted to the pediatric intensive care unit (PICU).[1–7] Approximately 50% and possibly more of the PICU-admitted children have been reported to be undernourished.[1,3,5,7] Undernourishment is associated with increased morbidity, mortality, and prolonged hospital stay.[1,3–7] Malnutrition may be evident on admission or acquired during the PICU stay.[1,5]

Despite the prevalence and negative association of malnutrition with PICU outcomes, its correction in PICUs is often delayed, as the acute physiologic needs of the critically ill garner more attention than nutrition support.[1–3,5,6] Critically ill patients may struggle with enteral feeding, which can lead to high gastric residuals, bacterial colonization, and increased risk of aspiration pneumonia. This often results in an association with ventilator-associated pneumonia (VAP).[8]

A study found that the protein-energy intake of its 240 study participants was significantly lower than that recommended by the American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines ($P<0.001$).[2] Only 40% of their participants received enteral nutrition (EN) on Day 2 of PICU admission. By Day 8, EN was started in 59% of study participants, parenteral nutrition in 20%, while intravenous (IV) fluids was the sole form of nutrition in approximately 20% of participants.[2]

However, nutrition in critically ill children admitted to PICUs is now gaining equal importance as the acute and critical physiologic needs of these children. ASPEN and the Society of Critical Care Medicines (SCCM) have laid down the best practices in nutrition therapy in critically ill children (>1 month and <18 years) admitted to PICUs.[6] EN, or providing nutrition through gastrointestinal (GI) tract, is recommended as the preferred route for nutrient delivery in critically ill children with intact GI tract.[1,6,9,10] Enteral nutrition provides essential micronutrients and macronutrients, meeting daily energy requirements of hospitalized patients. It has been shown to reduce hospital stay duration and decrease mortality in critically ill children.[10]

Though oral route is the most common form of EN, the term is usually used for enteral tube feeding (ETF) through nasogastric (NG) tube, gastrostomy tube, gastro-jejunostomy tube, or jejunostomy tube.[11] The majority of nutrition formulas available for ETF are isocaloric (1 kcal/mL).[9] ETF is known to cause gastric intolerance.[9,10,12] However, there is hardly any data on gastric intolerance of these formulae in pediatric patients admitted to PICUs.

Groviva® Advance is a scientifically designed isocaloric formula for pediatric patients requiring EN to provide nutrition based on energy expenditure and enhancing gastrointestinal function with dietary fibers and probiotics.

The aim of this study is to evaluate safety and gastrointestinal tolerance (product compliance) of Groviva® Advance in hospitalized pediatric patients requiring an isocaloric formula for enteral tube feeding.

Methods

Study Design

This prospective five-day single center, open-label, clinical study was conducted between July 2022 and December 2022 to evaluate the safety and gastrointestinal tolerance of Groviva® Advance in hospitalized pediatric patients that required isocaloric formula for enteral tube feeding. Before selecting participants, their demographic information and medical history were recorded. The patent for Groviva® Advance is held by Signutra Inc.

Inclusion Criteria

This study included pediatric patients aged 2-18, of any sex, with informed consent from their legal representatives, who were hospitalized for at least two days and required isocaloric enteral tube feeding.

Exclusion criteria

Pediatric patients <2 years or >18 years, who received a tube feeding before hospitalization; had any evidence of severe organ dysfunction or any clinically significant physical or clinical deviation from the normal which is a contraindication for enteral feeding; had a history of previous or established renal, hepatic, cardiovascular, respiratory, skin, hematological, endocrine, neurological, or gastrointestinal diseases; or had known protein intolerance or allergy to any of the constituents of Groviva® Advance were excluded from the study.

Intervention

Table 1 shows energy and nutrient requirements met by dissolving 45 grams of Groviva® Advance in 170 ml of water. Included participants were administered Groviva® Advance (45 grams in 170 milliliters of water; reconstituted amount 210 milliliters; equivalent to 200 kcal [1kcal in 1ml]) three hourly every day from Day 1 to the end of hospitalization or Day 5, whichever was earlier.

The treating doctors met the age-specific recommended daily energy and nutrient requirements by providing the requisite amount of Groviva® Advance in proportionate amounts of water.

Table 1: Nutritional Profile of Groviva® Advance

Nutrients	Unit	Per 100g Powder	Per Serving (45g)
Energy	kcal	471.0	212
Total Fat	g	23.5	11
Saturated Fat	g	5.0	2
MUFA	g	14.0	6
PUFA	g	4.6	2
Linoleic Acid (Omega-6)	g	3.6	2
Alpha - Linolenic Acid (Omega-3)	g	1.0	0
Trans Fat	g	0	0
Cholesterol	mg	1	0
Carbohydrates	g	47	21
Added Sugars	g	0	0
Dietary Fiber (AI)	g	3	1
Soluble Fiber	g	3.0	1
Prebiotic (FOS)	g	3.0	1
Protein*	g	16.5	7
Taurine	mg	45	20
L-Carnitine	mg	7.0	3

Inositol	mg	35	16
DHA	mg	45	20
Lactobacillus acidophilus **(1x10^8)**	CFU	1.6	1
Bifidobacterium lactis **(1x10^8)**	CFU	1.6	1
Vitamins			
Vitamin A*	mcg	395	178
Vitamin D*	IU	395	178
Vitamin E*	IU	8.2	4
Vitamin K*	mcg	37	17
Vitamin C*	mg	39	18
Folic acid*^	mcg	50	23
Vitamin B_1 (Thiamine)*	mg	0.5	0
Vitamin B_2 (Riboflavin)*	mg	0.8	0
Vitamin B_3 (Niacin)*	mg	5.5	2
Vitamin B_6*	mg	1	0
Vitamin B_{12}*	mcg	1.2	1
Pantothenic Acid* (AI)	mg	3.3	1
Biotin* (AI)	mcg	15	7
Choline	mg	130	59
Minerals			
Iron*	mg	11	5
Calcium*	mg	495	223
Phosphorus *	mg	700	315
Magnesium *	mg	90	41
Zinc *	mg	6	3
Iodine *	mcg	105	47
Copper*	mcg	630	284
Selenium*	mcg	27.0	12
Chromium*	mcg	18	8

Manganese*	mg	2.7	1
Molybdenum**	mcg	30	14
Sodium*	mg	120	54
Potassium*	mg	375	169
Chloride# (AI)	mg	210	95
*: ICMR RDA 2020; ʊ: RDA not established in Indian Council of Medical Research (ICMR)/World Health Organization (WHO) guidelines; ^: 1 mcg Food / Dietary Folate = 0.5 mcg of Synthetic Folic Acid; AI: Adequate Intake; MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids			

Endpoints

The study's primary endpoint was to assess the gastrointestinal tolerance and safety (product compliance) of Groviva® Advance. Gastrointestinal tolerance was assessed based on the episodes of diarrhoea, stomach irritation, regurgitation, abdominal bloating, and vomiting. Gastric residual volume (GRV) >500 ml/day was considered significant. GRV was measured before giving any scheduled feed at 0730 hours, 0900 hours, 1530 hours, and 1700 hours. Formula administration-related adverse events were recorded throughout the study.

The secondary endpoint was to assess the weight loss if any and abdominal girth between baseline and Day 5.

Statistical Analysis

R version 4.2.2 was used to analyse the data. Quantitative data was described as mean ± standard deviation (SD) and qualitative data as number and percentages. One way Analysis of Variance (ANOVA) was used to look for the change in mean weight and abdominal girth of the population from baseline (Day 1) to the end of the study (Day 5). P value <0.05 was considered significant.

Ethical compliance

The study was conducted according to the principles of the Declaration of Helsinki, and in compliance with the guidelines for good clinical practice by the International Conference of Harmonization. The study was approved by the Institutional Ethics Committee of "KIMS Ethics Committee, Secunderabad, India on 12th July 2022, confirmation no: KIMS/EC/2022187-02. The study was registered with the clinical trial registry of India as CTRI/2022/07/056542. Written informed consent was taken from the participants' legal guardians/representatives.

Results

Demographics

The study included 31 participants of average age (± SD) 9.17 ± 4.2 years; 64.25% males; of average weight 30.89 ± 16.55 kg; hospitalized in ICU for an average of 11.22 ± 5.51 days for various medical conditions as shown in **Table 2.** At admission, none of the participants had intestinal obstruction, gut malrotation, gastroenteritis, or gut sepsis.

All the study participants received pantoprazole for GI symptoms. Of these, one participant also received domperidone and azithromycin along with pantoprazole.

Table 2: Medical diagnosis for which participants were admitted to the Intensive Care Unit	
Medical diagnosis	**N (%)**
Dengue with dengue shock syndrome, dengue encephalopathy, hyperferritinemia with MODS, or DSS with LV dysfunction	10 (32.3%)
Pneumonia ± other conditions: very severe; influenza A pneumonia; influenza pneumonia with HT emergency; post pneumonectomy; WALRI, RSV pneumonia; VAP with status epilepticus	9 (29.0%)
AKI post HD, Uremic encephalopathy; AKI + heavy metal poisoning with ARDS	2 (6.5%)
Traumatic injury: Traumatic Abdominal injury with right Hemothorax; traumatic tracheal injury	2 (6.5%)
Encephalitis: Autoimmune; Acute necrotizing	2 (6.5%)
Liver related: Wilsons disease with liver failure; acute viral hepatitis with pancreatitis	2 (6.5%)
Disseminated TB with TBM	1 (3.2%)
MISC with septic shock	1 (3.2%)
Stroke; post decompressive craniectomy	1 (3.2%)
Chronic lung disease with prolonged ventilation	1(3.2%)
AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; HD, hemodialysis; MISC, multisystem inflammatory syndrome; MODS, multiple organ dysfunction syndrome; TB, tuberculosis; TBM, tuberculous meningitis; RSV, respiratory syncytial virus; VAP, ventilator-associated pneumonia; WALRI, wheeze associated lower respiratory infection	

The various other medical findings (clinical or laboratory) present at admission are enumerated in **Table 3.**

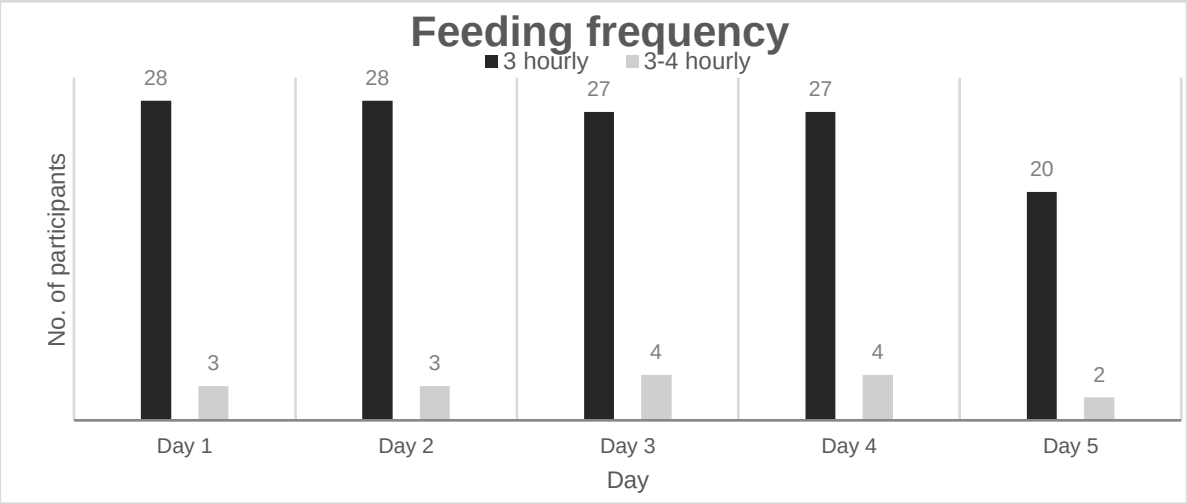
Table 3: Medical findings (clinical or laboratory) at admission	
Medical findings at admission	**N (%)**
Ascites/abdominal distension	17 (54.8%)
• Mild ascites	15 (88.2%)
• Mild to moderate ascites	1 (5.9%)
• Ascites +acute kidney injury*	1 (5.9%)
Liver issues	16 (51.6%)
• Mild transaminases increase	12 (75%)

• Moderate transaminases increase	1 (6.3%)
• Admitted for Wilson Disease	1 (6.3%)
• Admitted for traumatic liver injury grade 3	1 (6.3%)
Gastrointestinal bleed (including one oral bleed)	3 (9.7%)
Mild constipation	2 (6.5%)
Mild pancreatitis	1 (3.2%)
*Admitted for acute kidney injury	

Groviva® Advance feeding details

The majority of participants received the Groviva® Advance tube feed three-hourly on all five days of the study (**Figure 1**).

Figure 1: Frequency at which Groviva® Advance tube feed was given.



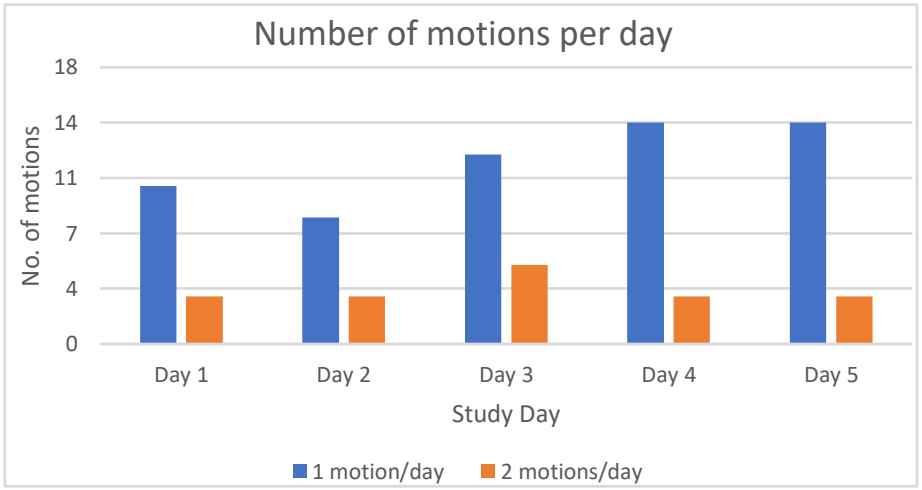
Taking 45 grams of Groviva® Advance in 170 ml of water as one feed, the total number of feeds given per subject per day were calculated. The average number of feeds per day is shown in **Table 4.** The average range of total feeds varied from 295.16 ± 275.19 to 1074.737 ± 347.94 mL per day. Data for the total number of feeds was not available for eight subjects on Day 5. One patient succumbed to disease-related complications, and another was nil orally on Day 5 due to a scheduled surgery.

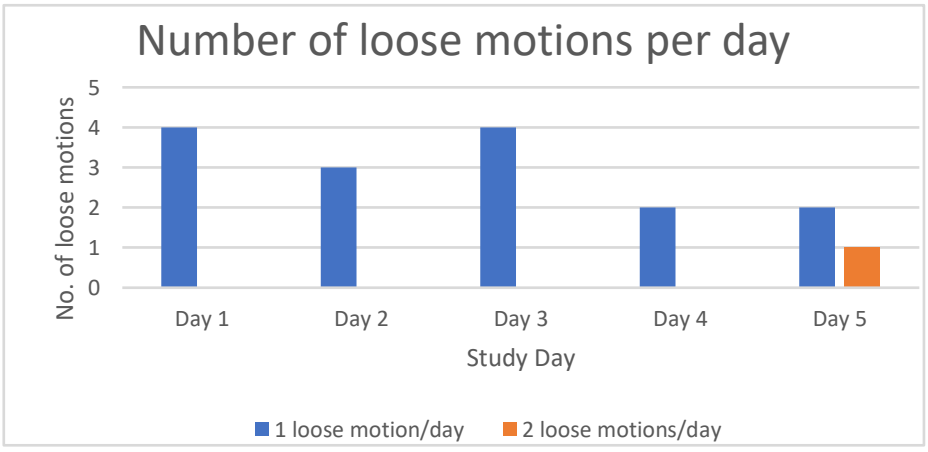
Table 4: Average volume of feeds per day	
Day	Quantity of feeds ± standard deviation (mL)
Day 1	295.16 ± 275.19
Day 2	478.06 ± 342.34
Day 3	748.06 ± 392.55
Day 4	936.06 ± 392.73
Day 5	1074.737 ± 347.94

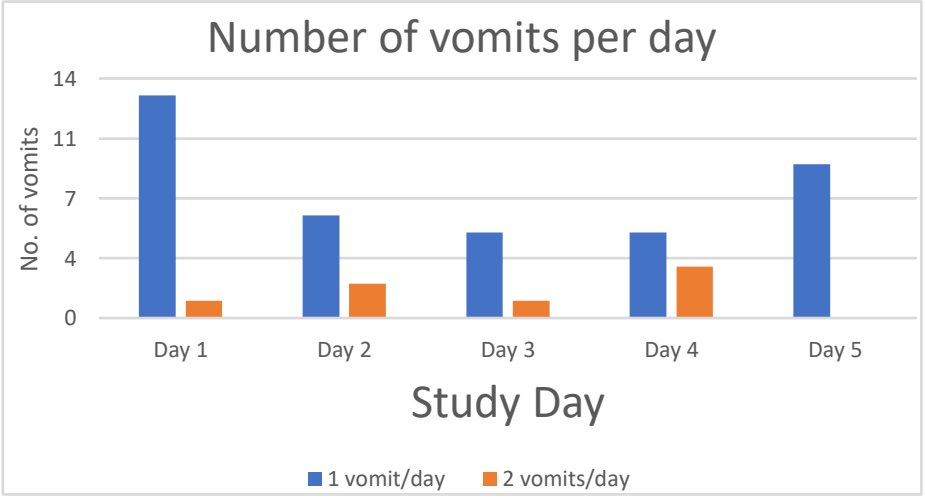
Gastrointestinal Tolerance

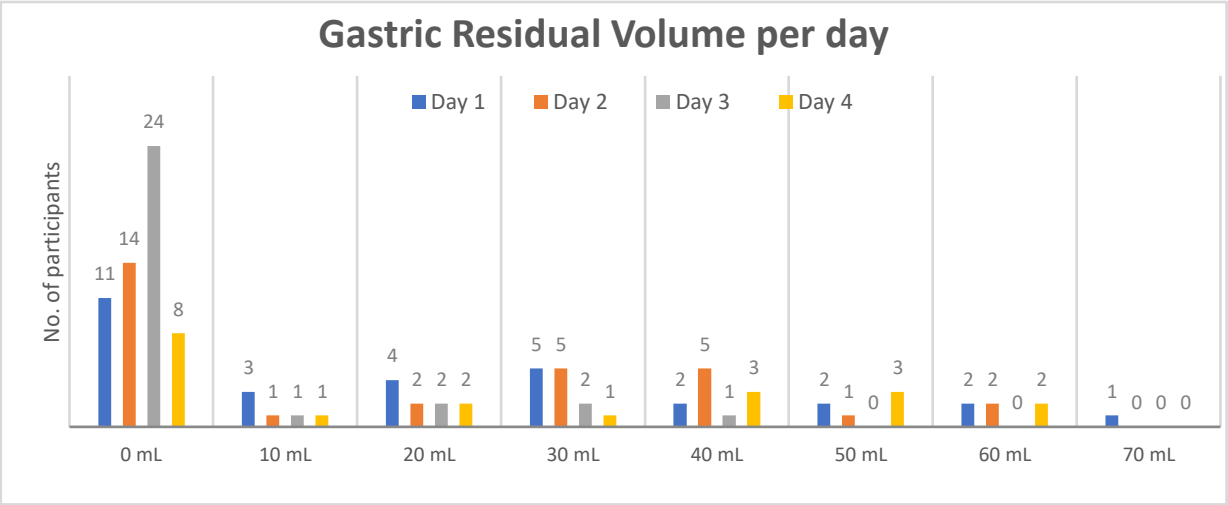
The majority of subjects did not experience any gastrointestinal symptoms. In general, the subjects had one motion per day. Only one subject passed stool five times on Day 3 (not shown in figure), but the stools were not loose. Subjects who had loose stools, usually had only one loose stool per day. Some subjects experienced one episode of vomiting per day (**Figure 2**). There was minimal or no total daily aspiration or GRV (**Figure 2**). Only one participant with lung disease on chronic ventilation had aspiration of 100 mL and 120 mL on Day 1 and Day 2, respectively, and 90 mL, 80 mL and 50 mL on Days 3, 4 and 5 respectively (not shown in figure). No patient had GRV >500 ml/day (more than 5ml/kg). One participant had deceased on Day 5, one was nil orally due to a scheduled surgery and data was not available for eight patients.

Figure 2: Gastrointestinal symptoms and gastric residual volume after the administration of Groviva® Advance tube feed. No patient had gastric residual volume >500 ml/day.









Effect of Groviva® Advance on weight and abdominal girth

The ANOVA analysis showed no statistically significant change in weight (P=0.7163) and abdominal girth (0.6381) of study participants. No weight loss was observed.

Administration of formula

There were no issues encountered during the preparation and administration of Groviva® Advance. No problems were encountered during the mixing of Groviva® Advance with water, or administration of the feed. The feeding formulation was of uniform thickness/consistency and no blockage of the NG tube was encountered.

Discussion

Groviva® Advance, an isocaloric formula for enteral feeding is associated with good gastrointestinal tolerance and safety profile in PICU patients.

Extended protein breakdown during illness can cause a protein deficit, leading to weight and lean body mass loss in children.[13] The increased metabolic demands due to illness or injury increase the protein-energy requirement over and above the basal metabolic need. In a prospective multicenter cohort study including PICU patients, it was found that the delivery of > 60% of the desired protein intake was associated with lower odds of mortality[14] Therefore, providing sufficient protein during critical illness is essential. EN is the preferred method of increasing nutrition in these children.

Isocaloric enteral nutrition (1 kcal/mL) helps address protein-energy imbalances.[15] Usually, an isocaloric nutrition formula is given with the help of an NG tube. In this study, Groviva® Advance isocaloric nutrition formula was given as ETF in a quantity decided by the treating doctor. ETF is known to cause gastric intolerance, identified by symptoms such as nausea/vomiting, diarrhea, abdominal distension/, or by two or more measurements of GRV > 3 mL/kg[9,10,12]. GI intolerance can be a limiting factor in providing nutrition through this route.[5,12] Formula-related gastric intolerance can be caused by the constituents of the formula, frequency, duration, and volume of feeds.[16]

In our study, large quantities of Groviva® Advance ETF could be safely administered over a period of five days and there were no administration issues (mixing, feeding, consistency) and only minimal episodes of diarrhea or vomiting. There was no case of NG obstruction as well. This can be attributed to dietary fibers and the dual probiotic formula of Groviva® Advance. Literature evidence showed that enteral formula enriched with soluble fiber and probiotics was safe and well tolerated by enterally tube-fed children with a range of critical conditions[17,18]

GRV remains one of the important factors in determining GI intolerance of ETF.[12] The study considered a GRV >500mL (GRV more than 5 ml/kg

or more than 50% of previous feed) as significant. However, all subjects had a GRV of <100 mL per day (1 ml/kg) except one subject on prolonged ventilation who had a GRV of 100-120 mL (1.2 ml/kg) on Day 1 and Day 2. Though, routine GRV assessment is no longer recommended as an ETF GI tolerance guidance in critically ill children,[12,19] it can be used as a guide for GI intolerance as per the PICU ETF feeding protocol.[9]

Abdominal distention is a typical late indication of non-occlusive bowel necrosis linked to early enteral nutrition.[20] Abdominal girth measurement helps assess abdominal bloating and distension. In our study, there was no statistically significant change in abdominal girth during the study period which is an important finding because 54.8% of the study participants had ascites/abdominal distension at the time of admission to the PICU.

While Groviva® Advance did not significantly improve patients' weight status, it positively impacted treatment outcomes by avoiding major clinical complications, mortalities, or adverse events in the study.

Conclusion

The study shows that Groviva® Advance is safe and well tolerated Enteral Tube Feed in critically ill children admitted to PICUs.

Limitation

One main limitation of the study is the short follow-up period, which leaves the long-term clinical effects of using Groviva® Advance as an enteral tube supplement uncertain.

Ethics Compliance:

The study was conducted according to the principles of the Declaration of Helsinki, and in compliance with the guidelines for good clinical practice by the International Conference of Harmonization. The study approved by the Institutional Ethics Committee of "KIMS Ethics Committee, Secunderabad, India on 12th July 2022, confirmation no: KIMS/EC/2022187-02. The study was registered with the clinical trial registry of India as CTRI/2022/07/056542. Written informed consent was taken from the participants' legal guardians/representatives.

Conflict of Interest Statement:

None

Acknowledgments Statement:

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work, and have given final approval for the version to be published. The authors thank Dr. Punit Srivastava and Dr. Kokil Mathur of Mediception Science Pvt. Ltd (www.mediception.com) for providing medical writing support in the preparation of this manuscript.

References:

1. Brown AM, Carpenter D, Keller G, Morgan S, Irving SY. Enteral Nutrition in the PICU: Current Status and Ongoing Challenges. *J Pediatr Intensive Care*. 2015;4(2):111-120. doi:10.1055/s-0035-1559806

2. Kyle UG, Jaimon N, Coss-Bu JA. Nutrition Support in Critically Ill Children: Underdelivery of Energy and Protein Compared with Current Recommendations. *J Acad Nutr Diet*. 2012;112 (12):1987-1992. doi:10.1016/j.jand.2012.07.038

3. Bagri NK, Jose B, Shah SK, Bhutia TD, Kabra SK, Lodha R. Impact of Malnutrition on the Outcome of Critically Ill Children. *Indian J Pediatr*. 2015;82(7):601-605. doi:10.1007/s12098-015-1738-y

4. Teka SG, Kebede RA, Sherman C. The prevalence of malnutrition during admission to the pediatric intensive care unit, a retrospective cross-sectional study at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. *Pan Afr Med J*. 2022;41:77. doi:10.11604/pamj.2022.41.77.31284

5. Moreno YMF, Ventura JC, Oliveira LD de A, Silveira TT, Hauschild DB. Undernutrition in critically ill children. *Pediatr Med*. 2020;3(0). doi:10.21037/pm-20-66

6. Mehta NM, Skillman HE, Irving SY, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Pediatric Critically Ill Patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition. *JPEN J Parenter Enteral Nutr*. 2017; 41(5):706-742. doi:10.1177/0148607117711387

7. Albadi MS, Bookari K. Is Undernutrition Associated With Deterioration of Outcomes in the Pediatric Intensive Care Unit (PICU): Systematic and Meta-Analysis Review. *Front Pediatr*. 2022;10: 769401. doi:10.3389/fped.2022.769401

8. Altintas ND, Aydin K, Türkoğlu MA, Abbasoğlu O, Topeli A. Effect of Enteral Versus Parenteral Nutrition on Outcome of Medical Patients Requiring Mechanical Ventilation. *Nutr Clin Pract*. 2011;26(3):322-329. doi:10.1177/0884533611405790

9. Kratochvíl M, Klučka J, Klabusayová E, et al. Nutrition in Pediatric Intensive Care: A Narrative Review. *Children*. 2022;9(7):1031. doi:10.3390/children9071031

10. Irving SY, Albert BD, Mehta NM, Srinivasan V. Strategies to optimize enteral feeding and nutrition in the critically ill child: a narrative review. *Pediatr Med*. 2022;5:9-9. doi:10.21037/pm-21-6

11. Jamieson NC, Tadi P. Feeding Tube. In: *StatPearls*. StatPearls Publishing; 2024. Accessed June 2, 2024. http://www.ncbi.nlm.nih.gov/books/NBK559044/

12. Tume LN, Valla FV, Joosten K, et al. Nutritional support for children during critical illness: European Society of Pediatric and Neonatal Intensive Care (ESPNIC) metabolism, endocrine and nutrition section position statement and clinical recommendations. *Intensive Care Med*. 2020;46 (3):411-425. doi:10.1007/s00134-019-05922-5

13. Hulst JM, Goudoever JB van, Zimmermann LJI, et al. The effect of cumulative energy and protein deficiency on anthropometric parameters in a pediatric ICU population. *Clin Nutr*. 2004;23(6): 1381-1389. doi:10.1016/j.clnu.2004.05.006

14. Mehta NM, Bechard LJ, Zurakowski D, Duggan CP, Heyland DK. Adequate enteral protein intake is inversely associated with 60-d mortality in critically ill children: a multicenter, prospective, cohort study1. *Am J Clin Nutr*. 2015;102(1):199-206. doi:10.3945/ajcn.114.104893

15. Ribeiro LMK, Oliveira Filho RS, Caruso L, Lima PA, Damasceno NRT, Soriano FG. Adequacy of energy and protein balance of enteral nutrition in intensive care: what are the limiting factors? *Rev Bras Ter Intensiva*. 2014;26(2). doi:10.5935/0103-507X.20140023

16. Wanden-Berghe C, Patino-Alonso MC, Galindo-Villardón P, Sanz-Valero J. Complications Associated with Enteral Nutrition: CAFANE Study. *Nutrients*. 2019;11(9):2041.

doi:10.3390/nu11092041

17. Simakachorn N, Bibiloni R, Yimyaem P, et al. Tolerance, Safety, and Effect on the Faecal Microbiota of an Enteral Formula Supplemented With Pre- and Probiotics in Critically Ill Children. *J Pediatr Gastroenterol Nutr*. 2011;53(2):174-181. doi:10.1097/MPG.0b013e318216f1ec

18. Evans S, Daly A, Davies P, MacDonald A. Fibre content of enteral feeds for the older child. *J Hum Nutr Diet*. 2009;22(5):414-421. doi:10.1111/j.1365-277X.2009.00991.x

19. Singer P, Blaser AR, Berger MM, et al. ESPEN guideline on clinical nutrition in the intensive care unit. *Clin Nutr Edinb Scotl*. 2019;38(1):48-79. doi:10.1016/j.clnu.2018.08.037

20. Marvin RG, McKinley BA, McQuiggan M, Cocanour CS, Moore FA. Nonocclusive bowel necrosis occurring in critically ill trauma patients receiving enteral nutrition manifests no reliable clinical signs for early detection. *Am J Surg*. 2000; 179(1):7-12. doi:10.1016/S0002-9610(99)00261-5